



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 65

Alan R. Katritzky

Advances in

Heterocyclic Chemistry

Volume 65

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Advances in

HETEROCYCLIC CHEMISTRY

Edited by

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Volume 65



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Preface

Volume 65 opens with a chapter by O. Meth-Cohn (University of Sunderland, UK) on the tertiary amino effect. This chapter updates a review on these interesting and initially unexpected reactions of tertiary anilines bearing *ortho* substituents by the same author together with Hans Suschitzky that appeared in Volume 14 of this series in 1972.

In Chapter 2, M. Bohle and J. Liebscher (Humboldt University, Berlin) review ring contractions of heterocycles by sulfur extrusion, which includes the elimination of various sulfur species all leading to a ring contraction containing one less member. This is the first comprehensive review of a subject that is of preparative as well as theoretical importance.

The volume continues with a contribution by A. F. Khlebnikov, M. S. Novikov, and R. R. Kostikov (all of St. Petersburg State University, Russia) on the role of carbenes and carbenoids in the synthesis of heterocycles. The application of carbenes to heterocyclic chemistry was covered in Volume 3 of our series in 1964 by C. W. Rees and C. Smithen, and subsequently in Volume 28 in 1981 by C. Wentrup. The present review covers the literature between 1979 and early 1995.

The next contribution, by Y. A. Ibrahim, A. H. M. Elwahy, and A. M. Kadry of Cairo and Zagazig Universities, Egypt, covers the synthesis, reactions, and biological activity of thienopyrimidines. It represents the first comprehensive account of these derivatives.

The final contribution, by K. Ohkata and K. Akiba (Hiroshima University, Japan), deals with reactions of pyrylium salts and pyrones, particularly reactions with nucleophiles and carbocyclic annulations. The literature is surveyed from 1980 on, thus bringing up to date some of the earlier material covered in Supplement Number 2 to *Advances in Heterocyclic Chemistry* by A. T. Balaban, G. W. Fischer, A. Dinuculescu, A. V. Koblik, G. N. Mezheritskii, and W. Schroth in 1982.

ALAN R. KATRITZKY

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The *t*-Amino Effect: Heterocycles Formed by Ring Closure of *ortho*-Substituted *t*-Anilines*

OTTO METH-COHN

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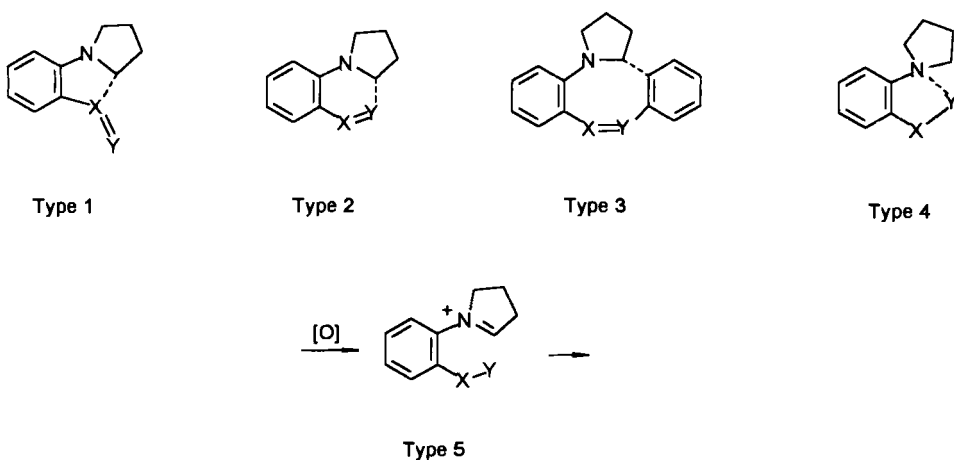
I. Introduction

The *t*-amino effect—the unexpected reactions of a tertiary aniline bearing an *ortho* substituent leading to cyclization—was reviewed in this series in

* Dedicated to my evergreen friend and mentor, Professor Hans Suschitzky, on his 80th birthday.

1972 [72AHC(14)211]. As is true of many of the most interesting reactions in chemistry, the bulk of the chemistry described here was discovered accidentally in the first case and then the underlying principle was developed. The first example of the *t*-amino effect was recorded 100 years ago by Pinnow (1895CB3039). Since our last review, a considerable body of important chemistry has been published on the application of this principle, notably by Verboom and Reinhoudt's group (90RTC311). They have discovered a variety of new reaction types of the *t*-amino effect and applied them to key target syntheses. This review updates the work described earlier and classifies the reactions into five types.

The five types of *t*-amino-effect processes are distinguished by the size of the ring formed or by its mode of formation in the key step in the reaction (Scheme 1). Type 1 (5-membered ring formation), type 2 (6-membered ring formation), and type 3 (higher ring formation) reactions focus on the unsaturated *ortho* substituent, $X=Y$, the chemistry of which constitutes the bulk of the advances. The nature of this *ortho* substituent determines the section subdivision, the atoms in the double-bonded group appearing in periodic-table order. All reactions of these types are two-step processes, involving first hydrogen abstraction from the α position of the *t*-amino function followed by cyclization of a dipolar intermediate. Type 4 reactions allow either saturated or unsaturated functions in the XY group, with initial reaction of this group with the *ortho* nitrogen atom. Type 5 reactions involve an alternative oxidative formation of the key iminium ion, which then cyclizes with the *ortho* function. Type 3 reactions are the latest development and pregnant with possibilities.



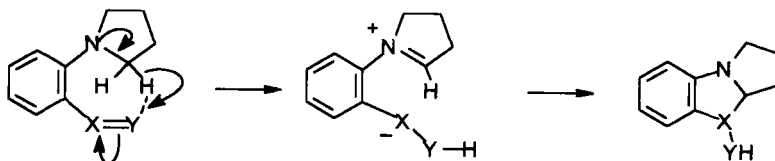
SCHEME 1

II. Type 1 Reactions: Formation of Five-Membered Rings from *t*-Amino-Effect Reactions

A typical example of the type 1 *t*-amino effect is shown in Scheme 2. All the reactions in this section proceed by an initial [1,6]H-shift from the α position of the tertiary amino group to the Y terminus of the *ortho* substituent. Subsequent cyclization of the dipolar intermediate leads to 5-membered heterocyclic products.

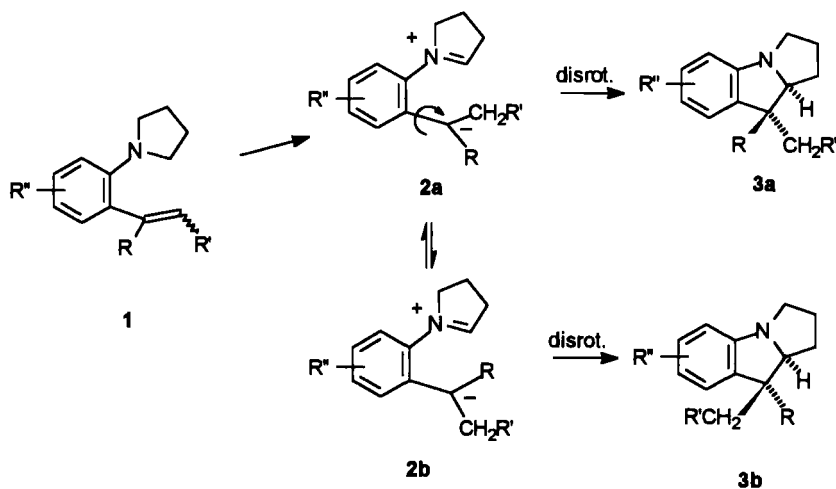
A. REACTIONS IN WHICH $X=Y$ IS $C=C$

In the previous review no examples of this important class of reaction were known. Their serendipitous discovery stemmed from Verboom and Reinhoudt's group studying the interaction of dimethyl acetylenedicarboxylate (DMAD) with enamines (see as follows).¹ Certain 2-vinyl-*N,N*-dialkylanilines (**1**) cyclize stereospecifically on heating to give pyrrolindoles (**3**) (Scheme 3) (82CC669; 84JOC269, 84TL2025; 85JOC3791, 85JOC3797). An α -electron-withdrawing group (e.g., $R = CO_2R$ or CN) was apparently essential, whereas a β -OMe group (R') slows the reaction and β -CN speeds it up. Polar solvents favor the process while hydrocarbons inhibit it, thus supporting the involvement of the dipolar intermediate **2**. The reaction is fast with the almost planar pyrrolidine derivatives and faster with 3-pyrrolines (85JOC3797) (owing to improved cation stabilization; however, side reactions may result from the tendency of pyrroline to aromatize), but very slow with piperidines (84JOC269). The reaction can be catalyzed with a Lewis acid (e.g., zinc chloride), yielding a mixture of *cis*/*trans* isomers **3a** and **3b** (this geometry refers to the disposition of bridge-head hydrogen relative to the adjacent electron-withdrawing group— CO_2R or CN), while the thermal process is stereospecific. These data support a



SCHEME 2

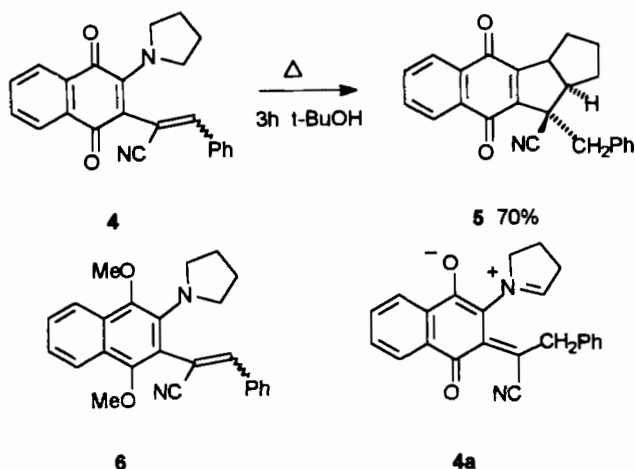
¹ During a lecture to the Grasmere Heterocyclic Symposium, Professor Reinhoudt disclosed his results but was not sure of the mechanistic rationale behind them. I was able to point him to our 1972 review.



SCHEME 3

two-step mechanism characteristic of the *t*-amino effect: An *antarafacial* [1,6]H-shift gives a dipolar intermediate **2a**, which cyclizes in a *disrotatory* manner to give **3a**. Polar solvents, planar rings, and conjugation all stabilize the polar species **2a**, and α -CN stabilizes the dipolar anionic center while a double bond or planar ring stabilizes the cationic charge. The first step is enhanced when a 1,4-quinone replaces the benzene ring (87MI1; 88JOC2278). Thus the benzoquinone **4** gives solely the *trans*-benzopyrroloindole **5** in 70% yield on refluxing for 3 h in *t*-butanol; however, the corresponding hydroquinone **6** did not cyclize, but decomposed after 2 weeks' reflux in alcohol or hydrocarbon solvents. The quinone carbonyl stabilizes the anionic center in the dipolar intermediate and appears to inhibit rotation of this group (see **4a**), ensuring formation of the *trans* isomer only (Scheme 4). [The possibility that the first step involved H abstraction by the C=O group (*q.v.*) was not considered by the authors.]

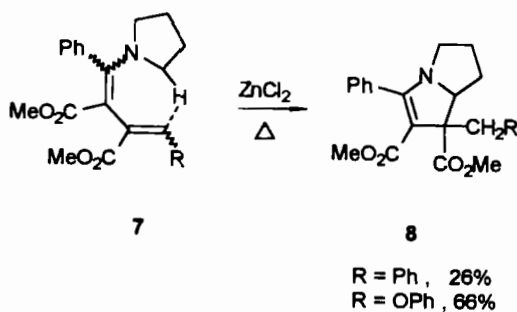
In a similar way, butadienylpyrrolidine analogs of the preceding systems, **7**, have been cyclized to give pyrrolizidines **8** by heating with zinc chloride in *t*-butanol or acetonitrile (Scheme 5) (78TL1351; 83JA4775). Related pyrrolizidines are formed in 78–95% yield by heating the adduct **10** of enamines **9** and DMAD in a protic solvent, the reaction proceeding by way of the same type of dipolar intermediate (Scheme 6) (82TL1217; 84JA1341). The reaction is rapid for the first two cases, **10a** and **10b**, proceeding directly to the pyrrolizidine at 0°C in methanol solution. The last case, **10c**, involving the pyrrolidine enamine of α -tetralone, proceeded slowly in aprotic media and allowed observation of the intermediate alkene



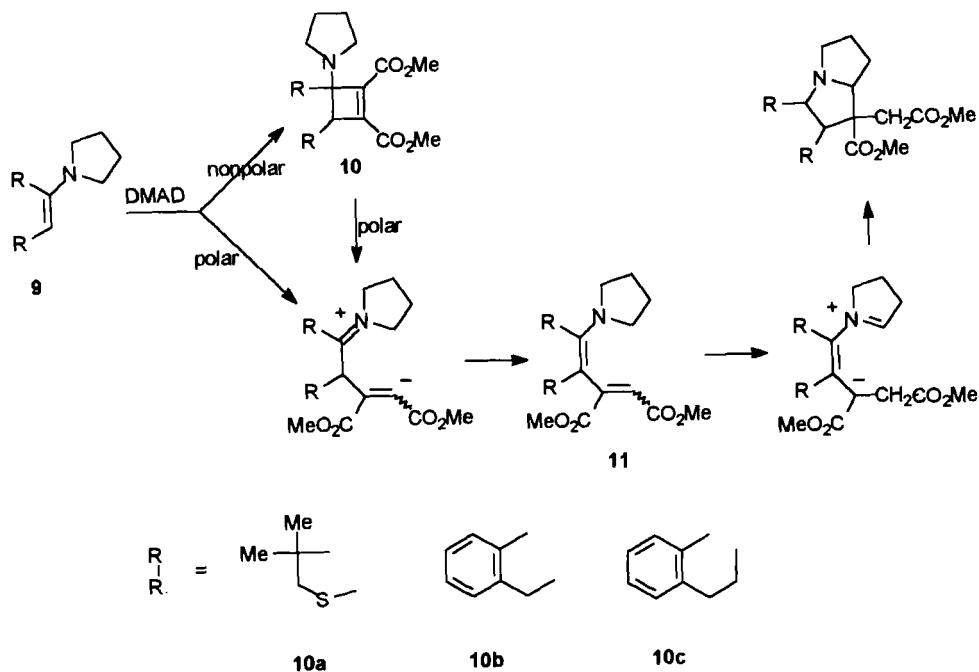
SCHEME 4

11 by NMR spectroscopy. Again, direct conversion to the pyrrolizidine was noted in methanol (81T3525).

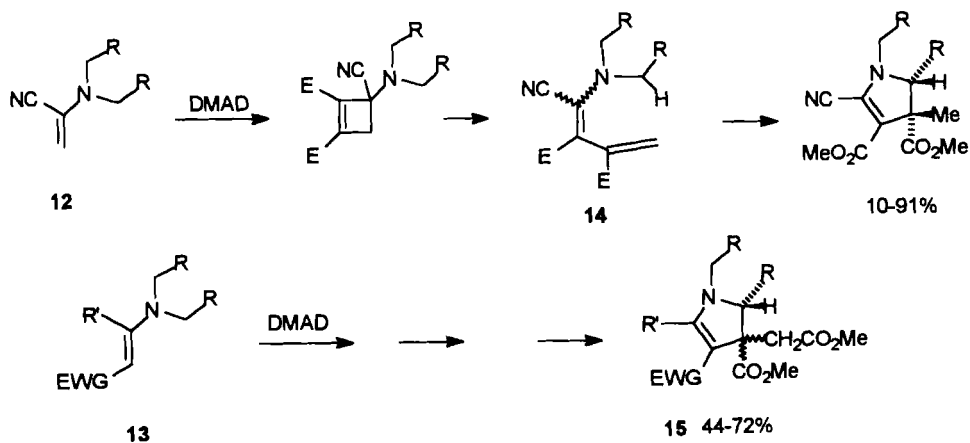
Viehe and co-workers (93BSB663; 94T7075, 94TL1185) have extended the DMAD reaction to simple acyclic enamines bearing an electron-withdrawing group (EWG) on either the α (**12**) or the β position (**13**), as shown in Scheme 7. Mechanistically, the reactions proceed exactly as in Verboom and Reinhoudt's examples, but with some surprising variations. The α -EWG series cyclized even at ambient temperature, yields of the product (solely the *trans* isomer) increasing with ring size in the case of the enamines of cyclic amines (5–37%; 6–40%; 7–85%; 8–90%). Although rate data were not reported, the 8-membered enamine apparently reacted fastest in the series, while the morpholine enamine was the least effective



SCHEME 5



SCHEME 6



$R = H, Me$ or $R-R = (CH_2)_2, (CH_2)_3, (CH_2)_4, (CH_2)_5, CH_2OCH_2$
 $EWG = CO_2Me, CO_2Et$
 $R' = H, Me, Ph$

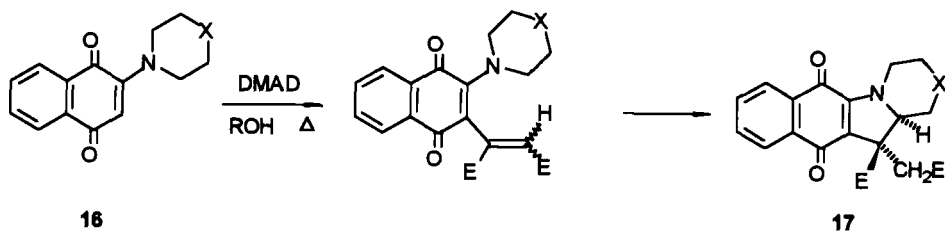
SCHEME 7

both in rate and yield (10%) terms. These data contrast with Verboom and Reinhoudt's findings that pyrrolidines were much more effective than piperidines. Enamines of acyclic amines were also effective, although at ambient temperature the diethylaminoenamine gave solely the acyclic isomer **14** ($R = H$) as product, which cyclized on heating. When one of the ethyl groups in this enamine was replaced by a phenethyl, the analogous acyclic product **14** ($R = Ph$) formed but did not cyclize on heating.

The β -EWG enamines, as expected from Verboom and Reinhoudt's observations (in their series, systems lacking an α -EWG did not cyclize in this manner—but see type 2 reactions!), require more vigorous conditions for cyclization, long heating in DMSO at 80–135°C being necessary with yields mysteriously improving in the presence of molecular sieves. (Added water has no deleterious effects!) Not surprisingly, under these conditions some reactions gave both *cis* and *trans* products **15**. Thus, while the diethylamino- and the piperidinoenamenes gave only *cis* products (44 and 67%, respectively) and the 7- and 8-membered enamines gave only *trans* products (52 and 59%), others gave mixtures. Clearly, steric factors are paramount in determining the preferred cyclization geometry of the dipolar intermediate, and these have been partially rationalized. At lower temperatures, the dienamine intermediate **14** (c.f. Verboom and Reinhoudt's observations) can be isolated in certain cases. Viehe has not studied the effect of solvents on these reactions, which could be interesting in the light of Verboom and Reinhoudt's findings.

It is clear that the considerable limitations noted by Verboom and Reinhoudt were largely due to the constraints imposed by the benzene or enamino ring. In Viehe's work on acyclic enamine reactions, the broad range of enamine bases, the ease of cyclization even in the absence of α -EWG groups, and the variation in product stereochemistry, all would appear to be the result of removing these constraints. Clearly, much remains to be done to exploit these observations fully.

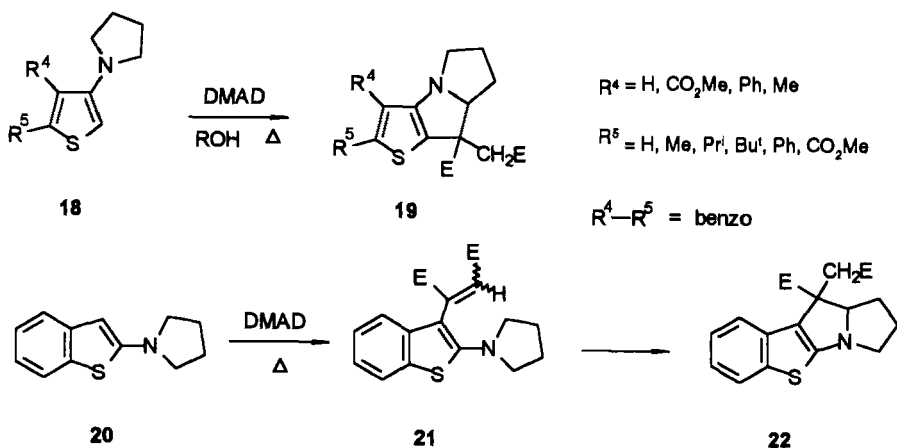
When the enamino naphthoquinones **16** were reacted with DMAD in refluxing methanol, the related pyrrolizidines **17** were again formed in 60–65% yield (Scheme 8) (79RTC251; 85SC1181). The corresponding benzoquinones did not undergo the Michael addition reaction, being insufficiently enamino. Even 3-pyrrolidinylthiophene **18** and -benzothiophene behaved as enamines with DMAD, giving fused pyrrolizidines **19** in 31–69% yield (Scheme 9) (81JOC424). 2-Pyrrolidinylbenzo[*b*]thiophene **20** similarly gave the corresponding fused pyrrolizidine **22**, but allowed isolation of the intermediate *E*- and *Z*-alkene intermediates **21** when the reaction was conducted in toluene solution (83JA4775). Typical of all this series, the reaction was faster in polar solvents, and while the use of toluene gave solely the *trans*-pyrrolizidine, polar solvents gave mixtures. Acetic acid as



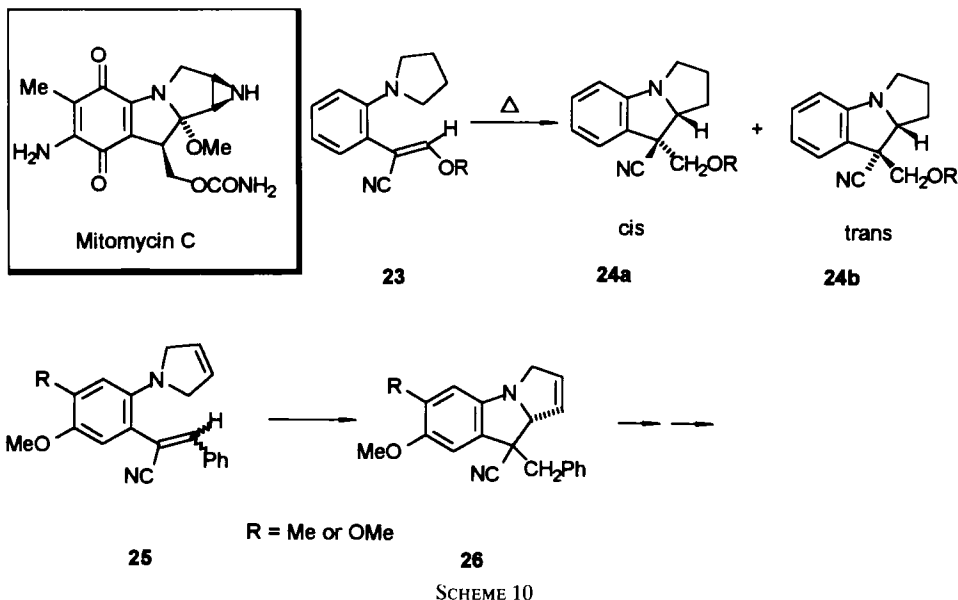
SCHEME 8

solvent, for example, gave a 94:6 ratio of *cis/trans* isomers. Furthermore the *E*-alkene cyclized more than 5 times faster than the *Z* isomer. By the use of deuterated derivatives (83JA4775), it was proved that the *H*-shift *and* the subsequent cyclization of the dipolar intermediate proceeded by way of a common helical geometry of the intermediate, this helix conformation being retained even after stereomutation of the dipolar species!

Type I reactions have been utilized to allow the synthesis of mitomycin C analogs, an important group of anti-tumor antibiotics (Scheme 10) (85JOC3791, 85JOC3797). The model compounds **23** were first shown to cyclize to a mixture of *cis* and *trans* isomers **24a** and **24b**; and as already demonstrated, the former was predominant in polar solution while the latter was preferred in nonpolar solvents. Thus the alkene **23** ($R = n\text{-Bu}$) gave a 73:9 mixture of *cis/trans* isomers in *n*-butanol while in mesitylene solution the ratio was 12:56. Other ethers studied included $R = \text{PhCH}_2$, Me, and MeOCH_2 . The benzyl ether group of the *trans* isomer was removed



SCHEME 9



with HBr and the necessary carbamate group readily introduced in good yield. Subsequent application of this methodology to closer analogs of mitomycin were then studied. In particular, the pyrroline derivative **25** was made and the isomers **26** separated, allowing functionalization of the key double bond. However, attempts to introduce the aziridine and the quinone functionality were not successful.

It is evident that although much is now known about these type I *t*-amino-effect reaction pathways involving C=C substituents, the synthetic applications have barely been touched. The predictable stereochemistry and remarkable specificity of the reactions await further development.

B. REACTIONS IN WHICH X=Y IS C=N

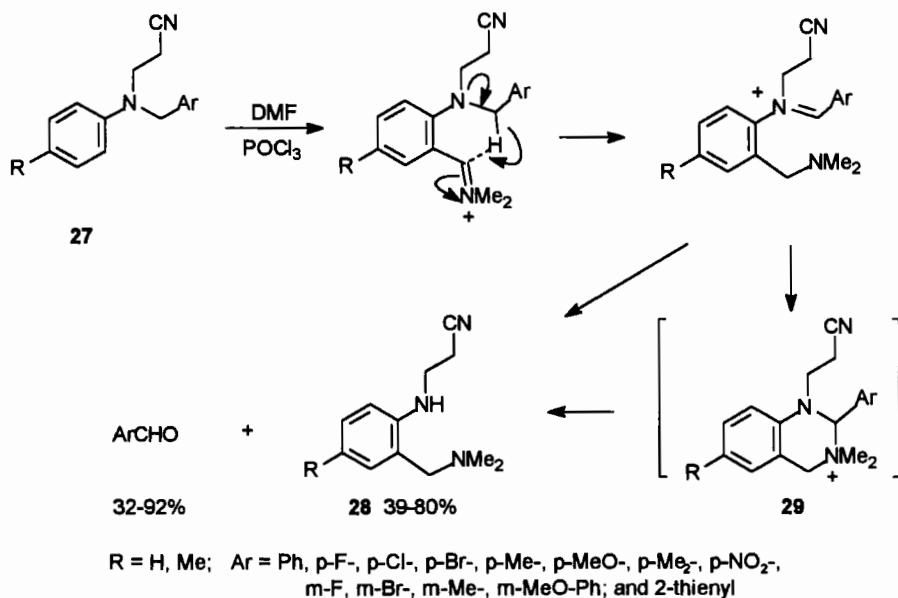
Only one example of this type was noted in the previous review—a reaction involving the photocyclization of quinonimines. During attempts to formylate *tert*-*p*-toluidines Shawcross and Stanforth (88T1461; 89T7063) observed *ortho*-dimethylamino methylation and dealkylation to give **28**.

The reaction proceeds according to the principles of the *t*-amino effect (Scheme 11). A wide range of substituted benzyl derivatives followed this pathway. Debenzylation rather than decyanoethylation occurred—a fact attributable to the stabilization of the iminium cation that occurs in the former process, whereas destabilization would result in the latter. Furthermore, the reaction gave low yields with cation-destabilizing benzyl groups such as nitro- and difluoro-substituted derivatives. In the absence of the *para*-methyl group, normal *para*-formylation occurred and the perfluorophenylmethyl derivative (**27**, Ar = C₆H₅) formylated normally in the *ortho* position. The quinazolinium intermediate **29** was mooted (see type 3 reactions for more information on this reaction).

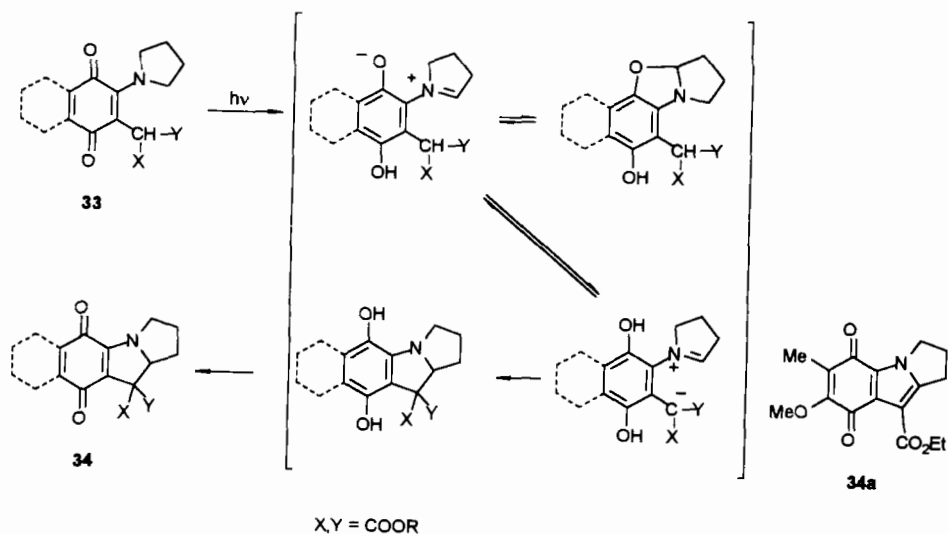
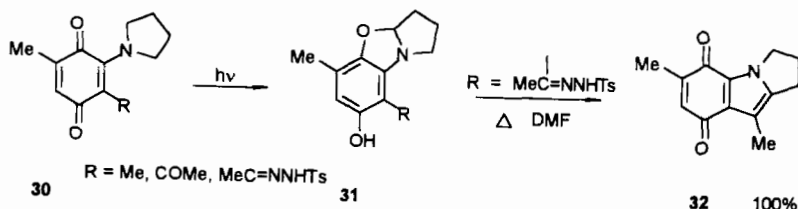
C. REACTIONS IN WHICH X=Y Is C=O

All the examples of this group in our first review involved 2-(*t*-amino)quinones. Further interesting examples of this type have been reported, while the involvement of ketones has also been noted.

The high-yield photocyclization of 2-pyrrolidinybenzoquinones **30** to give pyrrolooxazolidines **31** has been observed (Scheme 12) (77JOC3317).



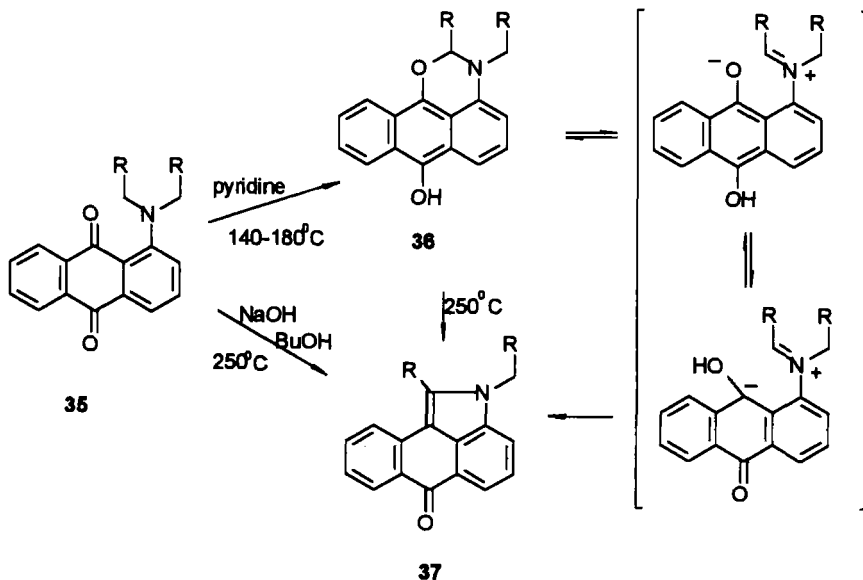
SCHEME 11



SCHEME 12

Akiba and co-workers [77H(6)1113, 77H(6)1773; 78H(9)1607; 78H(8)813, 78JOC4472; 81H(16)1579; 83CC817] noted that this reaction also proceeds thermally and that the oxazolidines undergo retrocyclization and recyclization, given an alternative adjacent substituent. Thus the oxazolidine **31** (R = CMeNNHTs) derived from the tosylhydrazide **30** (R = CMeNNHTs) is quantitatively transformed into the pyrroloindolequinone **32** [78H(8)1607, 78JOC4472]. They also observed a related novel photoreaction of benzoquinones and naphthoquinones **33** with an *ortho* "acidic" group [e.g., CH(CO₂R)₂], which gave indolizinoquinone **34** (Scheme 12) [77H(6)1113, 77H(6)1773; 78H(8)813; 81H(16)1579; 83CC817]. This process was applied to the one-step synthesis of an advanced 7-methoxymitosene precursor **34a** (83CC817).

The transformation of 1-dialkylaminoanthraquinones to oxazinoanthraquinones strictly falls into the type 2 reaction section, but was already covered in our earlier review. However, in a manner related to Akiba's



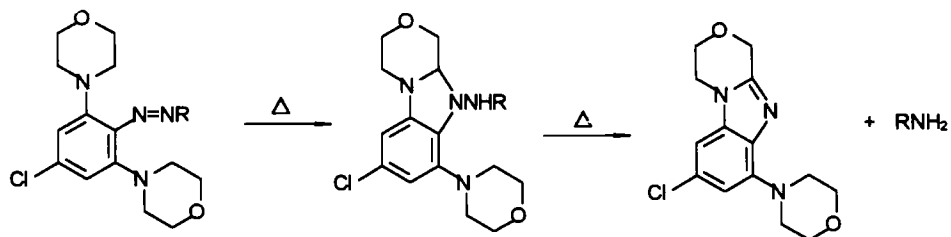
SCHEME 13

examples, the action of sodium hydroxide in butanol at 250°C on these oxazines **36** converts them or their precursors **35** into pyrroloanthracenes **37** (Scheme 13) (75KGS1360). Ring opening of 2-piperidino- and related naphthoquinones under photolysis was noted in the earlier review. Further work on this reaction has appeared [77H(6)1773].

D. REACTIONS IN WHICH $X=Y$ IS $N=N$

Azo compounds are very efficient in *t*-amino-effect reactions yielding benzimidazoles, and featured significantly in the previous review. Further work on transformation of the cobalt(II) complex of 2-dimethylaminoazobenzenes to *N*-methylbenzimidazole has shown that the azo compound converts ethanol to acetaldehyde [and cobalt(III) is formed] during the process [77JCS(D)872]. In a related manner, Kirschke (86TL4281) observed that attempts to recrystallize the azo compound **38** from ethyl acetate resulted in its conversion into the benzimidazole **40**, as shown in Scheme 14. When ethanol was used, the intermediate **39** was isolable.

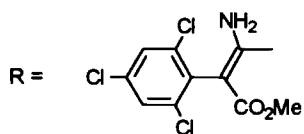
In a new type of reaction in this class, nitration of 4-amino-3-dialkylaminopyridines **41** results in pyridoimidazoles **43** [92H(34)1491] by way of 4-nitroamino derivatives **42** (Scheme 15). Yields were low (8–15%) and prod-



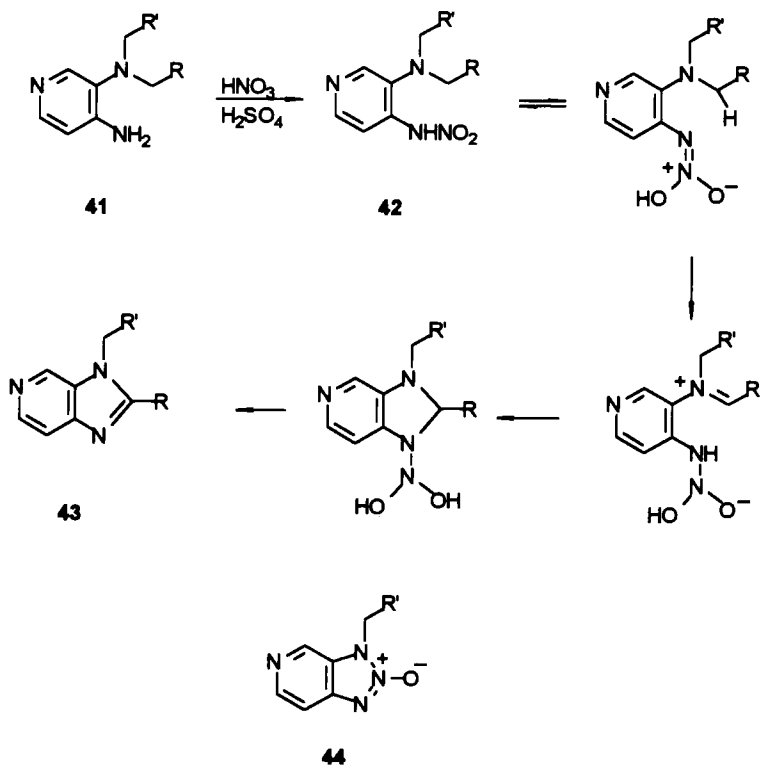
38

39

40



SCHEME 14



41

42

43

44

SCHEME 15

ucts of further nitration and oxidation were also observed, as well as a pyridotriazole **44** from type 4 chemistry (*q.v.*).

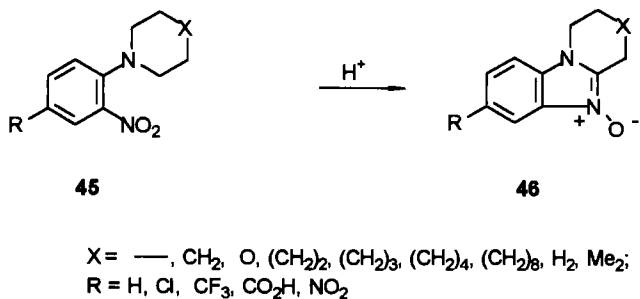
E. REACTIONS IN WHICH $X=Y$ IS $N=O$

The reactions of this group were the first type of *t*-amino effect noted in the literature and are well documented in the earlier review. Full details of the conversion of 2-nitro-*t*-anilines **45** into the corresponding benzimidazole *N*-oxides **46** (Scheme 16) have been published since the last review [73JCS(P1)696]. By-products include denitration and rearrangement of the nitro group from the 2 position to the vacant 4 position. *N*-(2-Nitrophenyl)dodecamethylenimine gave solely *N* = (2-nitrophenyl)- ω -chlorododecylamine in 90% yield on acid treatment. The benzimidazole or its *N*-oxide is formed on photolysis of the nitro-*t*-anilines by a different mechanism.

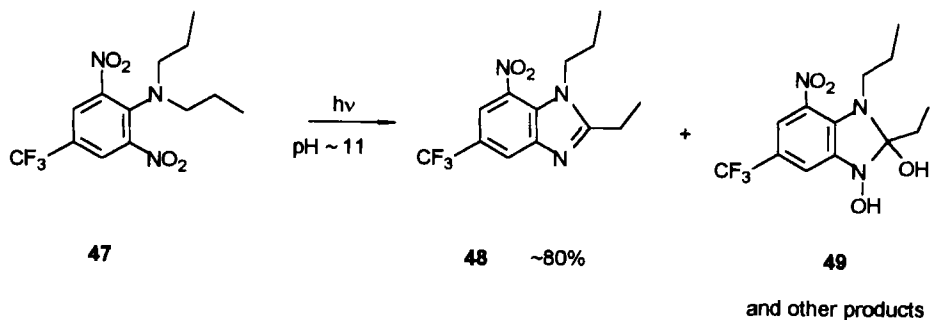
Dinitro-*t*-anilines constitute a major group of pre-emergent herbicides. The photodecomposition of these herbicides has been simulated by studying the photolysis of one typical example, Trifluralin **47** (74MI1). The major product from the action of sunlight in aqueous alkaline media was the benzimidazole **48**, and the by-products included the dihydroxybenzimidazole **49**, the benzimidazole *N*-oxide, and benzimidazoline derivatives of **48**, all being derived by *t*-amino-effect chemistry (Scheme 17).

The formation of benzimidazole *N*-oxides **51** from 2-nitro-*t*-anilines by the action of acid has been extended to *N*-(2-nitrophenyl)- and *N*-(3-nitro-2-pyridyl)tetrahydroisoquinolines **50** (95JHC529) (Scheme 18).

New methods for the synthesis of a new group of DNA-cleaving agents based on pyrrolbenzimidazoles and piperidinobenzimidazoles and of azamitomisenes, analogs of mitomycins, have been developed by Skibo and co-workers (90JOC3195; 91JMC2954, 91USP5015742; 93JMC3050; 94JMC78). The common skeleton **53** was synthesized utilizing the al-



SCHEME 16



SCHEME 17

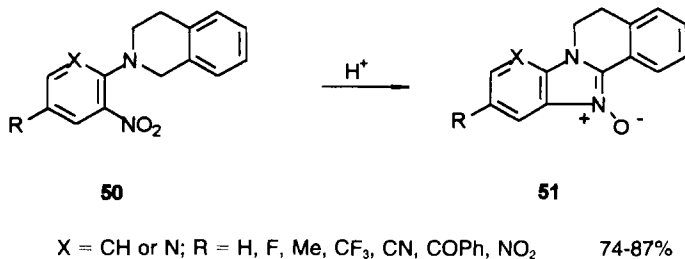
ready reported cyclization of 2-nitrophenylpyrrolidines **52** with zinc chloride in acetic anhydride (to give **53** R = OAc) [69JCS(C)70] or of 2-acetamidophenylpyrrolidines with performic acid (to give **53** R = H) (63JCS4666). In this way, advanced analogs **54**, **55**, and **56** have been developed; these compounds have been shown to be important new cytotoxic agents against melanoma cell lines, although they exhibit no activity against leukemia cell lines (Scheme 19).

Imidazoquinolones related to quinolone antibiotics have been generated by the same two cyclization approaches used by French workers (94JHC153) (Scheme 20).

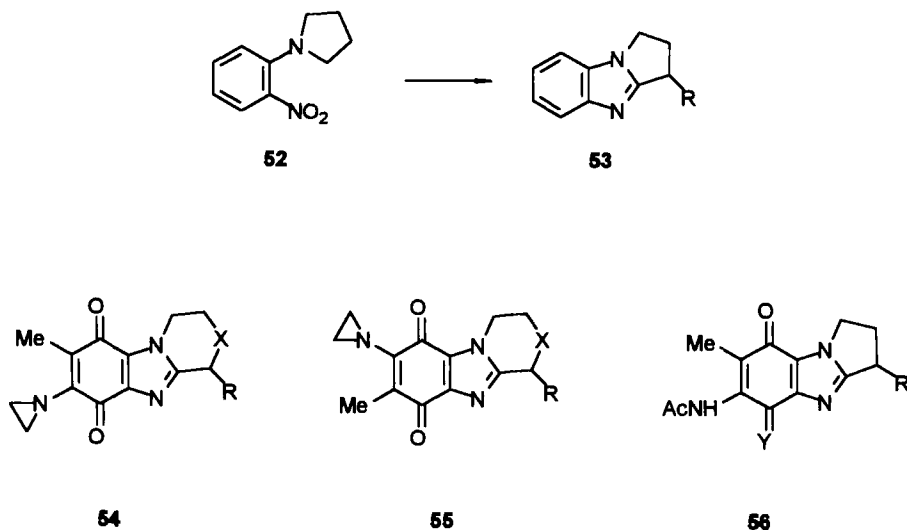
A remarkable transformation of nitroanilines **57** to *N*-alkyloxybenzimidazoles **58** under alkylation conditions (NaH/RCH₂X) has been shown to proceed by way of *N*-alkylation/cyclization/*O*-alkylation and is thus not a true example of a *t*-amino-effect process (95SC819, 95T4101) (Scheme 21).

F. REACTIONS IN WHICH X=Y IS N=S

The action of sulfonyl chloride on 2-aminophenyl-*t*-anilines **59** at ambient temperature is at once vigorous, clean, and unexpected, leading to tetrachlo-

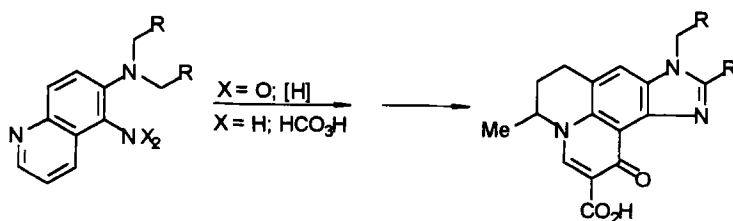


SCHEME 18

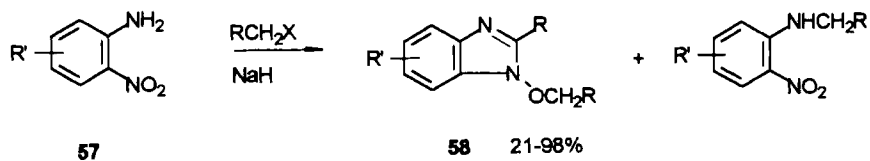


SCHEME 19

robenzimidazoles **60** (73TL4495) (Scheme 22). The reaction proceeds by a sequence of ring halogenation/sulfonylamine formation/cyclization, giving products of agrochemical interest [68JCS(C)1268]. The $\text{N}=\text{SO}_2$ group is clearly a highly efficient hydrogen (hydride) abstractor (at the SO_2 terminus) and anion stabilizing group on S. The reaction is equally effective for the conversion of the aminopyridine **61** or aminoquinoline **63** into the corresponding chlorinated fused imidazoles (**62** and **64**). 2-Amino-1-piperidinoanthraquinone is similarly converted into the corresponding 3-chloroimidazoanthraquinone in 40% yield. Interestingly, it would appear that the chlorination precedes cyclization, since benzimidazoles are only



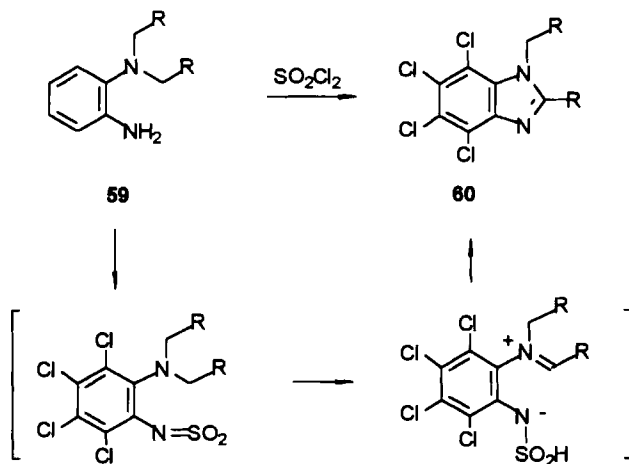
SCHEME 20



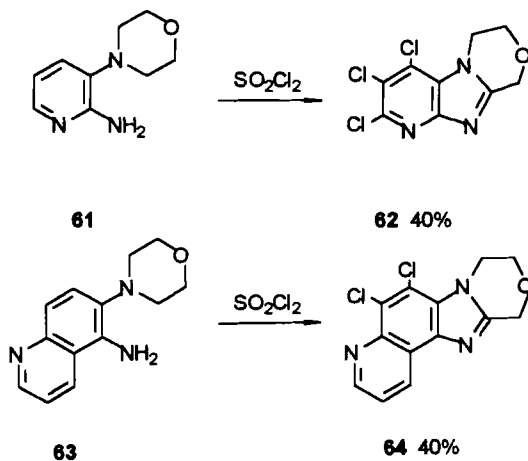
$R' = \text{H, 2-Me, 4Me, 4-Cl, 4-MeO, 4-NO}_2$

$R = \text{Me, Pr, Bu, Bn Allyl; X = Br or I}$

SCHEME 21



$R = \text{H, (CH}_2)_2, \text{CH}_2\text{OCH}_2, (\text{CH}_2)_3, (\text{CH}_2)_4$ 50-85%



SCHEME 22

partially chlorinated under these conditions, as are the more rapid cyclizing pyrrolidine derivative **59**, $RR = (CH_2)_2$.

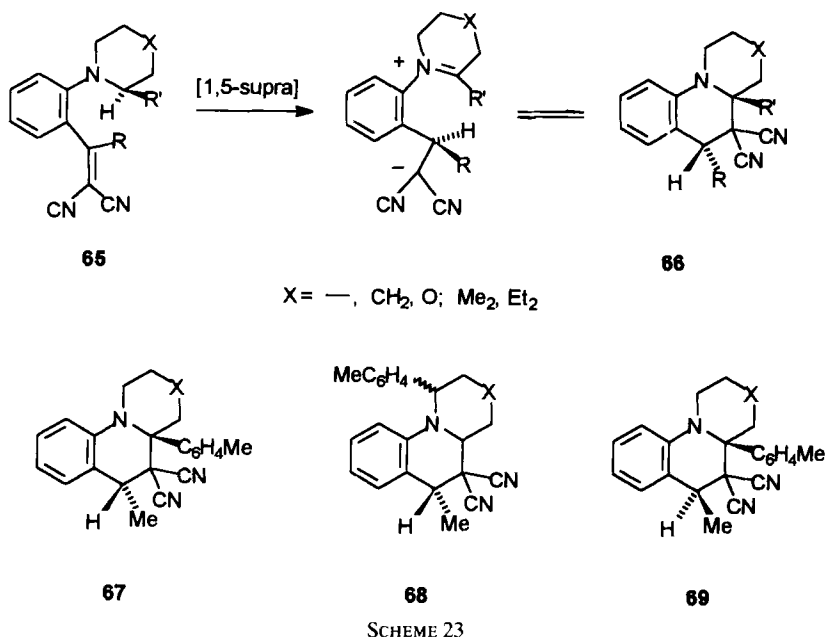
III. Type 2 Reactions: Formation of Six-Membered Rings from *t*-Amino-Effect Reactions

This category implies that the X substituent of the *ortho* group $X=Y$ abstracts the hydrogen from the *t*-aniline α position and that the group Y then cyclizes to the iminium carbon. Hence the anion-stabilizing character must reside at the Y position while the X group should be a hydride acceptor. In most other respects, the mechanism of the reaction is closely related to that of the type 1 reactions, with the same substituent and solvent effects operating. Surprisingly, it is rare to observe a mixture of pathways.

A. REACTIONS IN WHICH $X=Y$ IS $C=C$

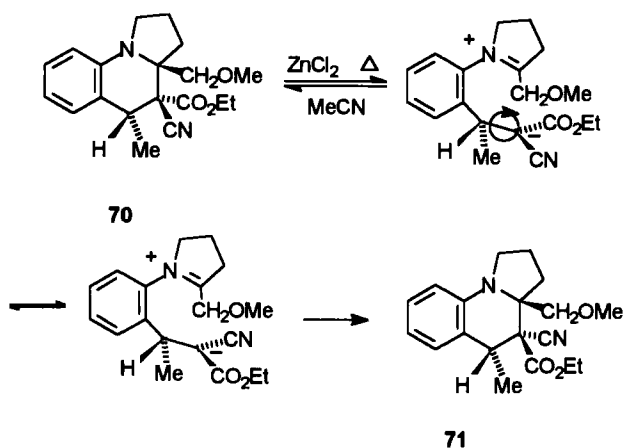
This group of reactions were first uncovered by Verboom and Reinhoudt and no examples appeared in the first review. They observed that when an *ortho*-vinyl-*t*-aniline bearing at least two anion-stabilizing groups at the Y position (e.g., **65**) was heated, it underwent cyclization to form a new 6-membered ring **66** (Scheme 23) (84JOC269; 87S641; 88T4637). In this series the cyclization was not limited to pyrrolidines, although the rate of cyclization decreased in the order pyrrolidine > piperidine > morpholine. Amazingly, not only did the reaction of α -substituted pyrrolidines take place regiospecifically (89JOC199) at the substituted site (which in the case of a methyl or aryl group stabilizes the cationic charge of the dipolar intermediate), but also homochiral starting material gave optically pure product of just the one diastereomer depicted (87JA3136; 89JOC209). These results showed that the cyclization step occurs exclusively at the same face from which the migrating hydrogen departs and that no rotation of the dipolar precursor occurs! Chirality of the precursor is transferred quantitatively to the product by way of a chiral helical dipolar intermediate.

Bulky groups such as methoxymethyl (which is also inductively destabilizing to a cation) resulted in mixtures of the two regioisomeric products from cyclization at the substituted and unsubstituted position. When the α substituent R' is an aryl group such as *p*-tolyl, despite its cation-stabilizing properties, the regio- and stereocontrol of the reaction is lost due to its bulk; thus three isomers **67**, **68**, and **69**, of the tricyclic product were isolated. While the first step of the cyclization process, the H abstraction, has been

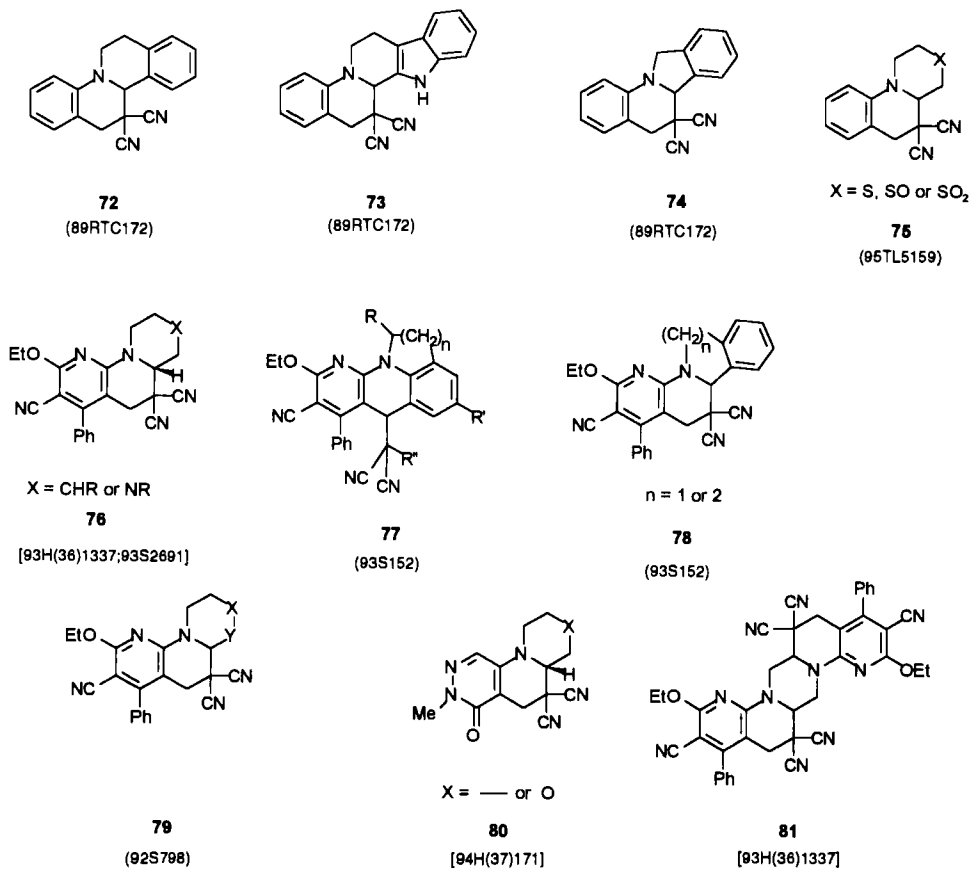


shown to be irreversible, the second cyclization step is thermally reversible. Thus, a variety of homochiral pyrroloquinoline products have been shown to epimerize (91RTC115) by the action of zinc chloride in refluxing acetonitrile. This epimerization reaction can be harnessed to good effect. For example, the homochiral *trans*-pyrroloquinoline **70** is converted to the enantiomerically pure *cis* isomer **71** since the large methoxymethyl prevents epimerization of the CCH_2OMe group (Scheme 24). In other cases, this group is also epimerized.

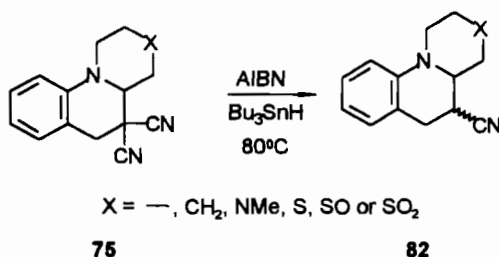
A variety of other systems (**72–81**) have been generated by cyclization of related β,β -dicycanoethylene derivatives (Scheme 25). The mode of cyclization of an indoline did not involve the *t*-amino effect, but rather an electrocyclization to the adjacent aromatic ring to give **77**. Gerlach has demonstrated that the geminal dicycano products **75** are readily and efficiently monodecyanated with AIBN and tributyltin hydride to give **82** (95TL5159), thus extending the synthetic utility of the series (Scheme 26). The stereochemistry of the resulting nitrile has not yet been clarified, but both diastereomers are produced, the major one (88:12) in the pyrroloquinoline being the *trans* isomer. No doubt, equilibration with base can be utilized. Thieno- and benzothienoindolizines and -quinolizines are formed when 3-dialkylaminothiophenes or 2- or 3-dialkylaminobenzothiophenes



SCHEME 24



SCHEME 25



SCHEME 26

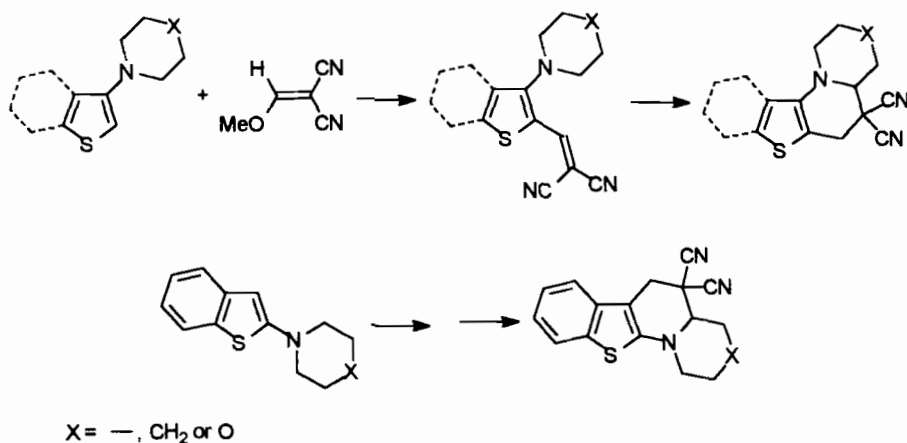
are treated with methoxymethylenemalononitrile followed by heating in butanol (Scheme 27) (90RTC481).

B. REACTIONS IN WHICH X=Y IS C=N

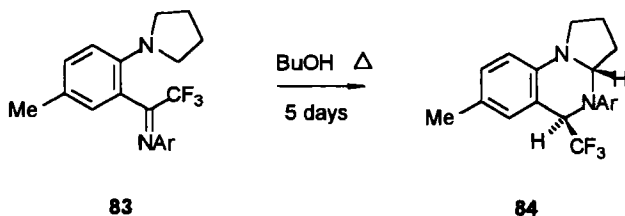
The only example of this new class of reaction is the conversion of imines of *N*-(2-trifluoroacetylphenyl)pyrrolidines to diastereomerically pure pyrroloquinazolines by heating in butanol for 5 days (Scheme 28) (84TL4309).

C. REACTIONS IN WHICH X=Y IS C=O

The above cyclization of an imine proceeds even more effectively for the parent ketone. When the ketones **85** are refluxed in butanol, a mixture



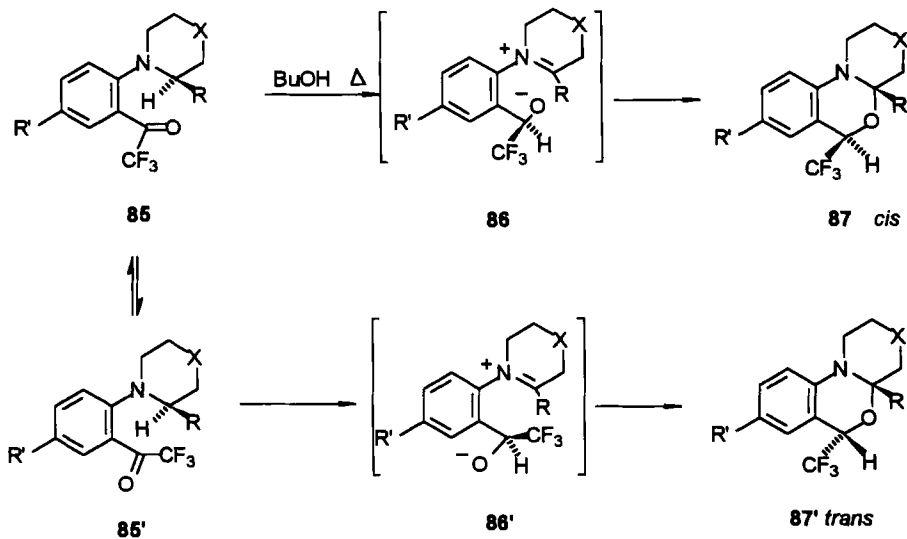
SCHEME 27



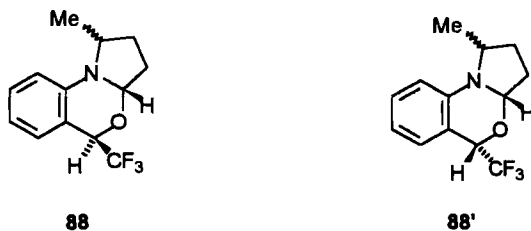
Ar = *p*-tolyl 66%

SCHEME 28

of *cis* and *trans* pyrrolo- and pyridooxazines **87** and **87'**, respectively, results in 70–95% yield (Scheme 29) (83TL3923; 89RTC147). The trifluoro group is essential for cyclization to proceed, the acetyl or methoxalyl groups being



R = H, Me, or CH₂OMe; X = —, CH₂; R' = H, Me, OMe

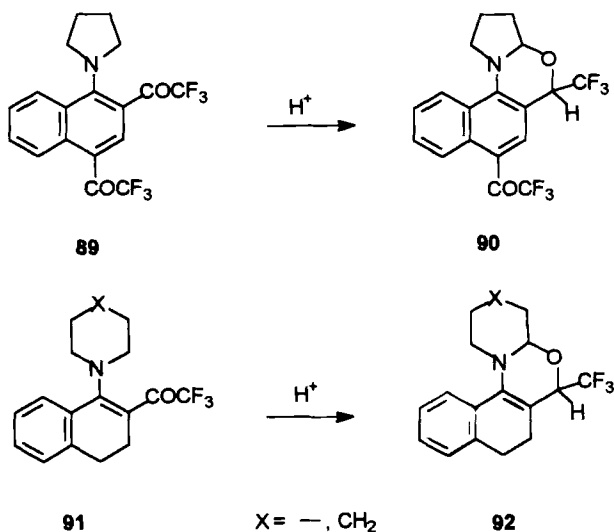


SCHEME 29

ineffective. The *cis/trans* ratio is dependent on the nature of heterocyclic groups X and R. As with the C=C cyclizations, the homochiral derivatives (**85**, R = Me and X = —) gave enantiomerically pure pyrrolobenzoxazine **87** (70%) together with the isomers **88** and **88'**, showing once again that the dipolar intermediates **86** and **86'** were formed uniquely by transfer of H to the same face of the ketone carbonyl and that the intermediate does not stereomutate to the alternative rotamer prior to cyclization. The *cis* and *trans* isomers are formed from the appropriate ketone conformer as illustrated.

Japanese workers (88TL4599) have shown that the acid-catalyzed (even silica gel) cyclization of the analogous pyrrolidinonaphthalenes **89** proceeds in high yield to give the pyrrolooxazines **90**—though, surprisingly, they were unable to cyclize the related benzene derivatives (Scheme 30) (however, this work was done before Verboom and Reinhoudt's results were reported). Verboom and Reinhoudt (82JOC3339) had earlier shown that the α -tetralone enamines **91** also underwent thermal or acid-catalyzed cyclization to give pyrrolidino- (53%) and piperidinoxazines **92** (44%) (Scheme 30).

The cyclization of 1-dialkylaminoanthraquinones (75KGS1360) was thoroughly reported in the earlier review and referred to in Section II.D of this review. Further examples of the dealkylation of 1-dialkylaminoanthraquinones during their synthesis have been reported by Zielske (87JOC1305), who showed that the 1- and 1,4-tosyloxanthraquinones are preferred intermediates for the corresponding dialkylamino derivatives.



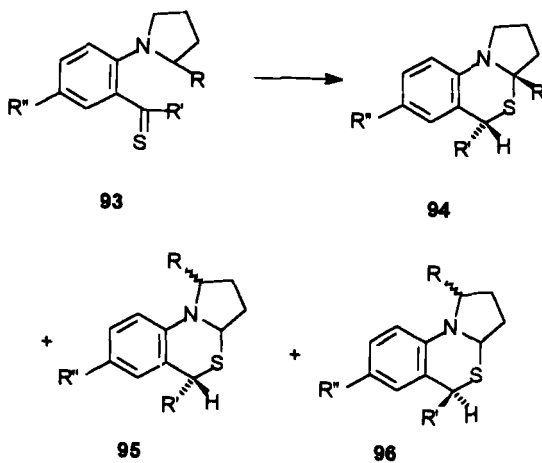
SCHEME 30

However, the higher temperature needed to introduce the second amino function causes some dealkylation by way of the *t*-amino effect.

D. REACTIONS IN WHICH $X=Y$ IS $C=S$

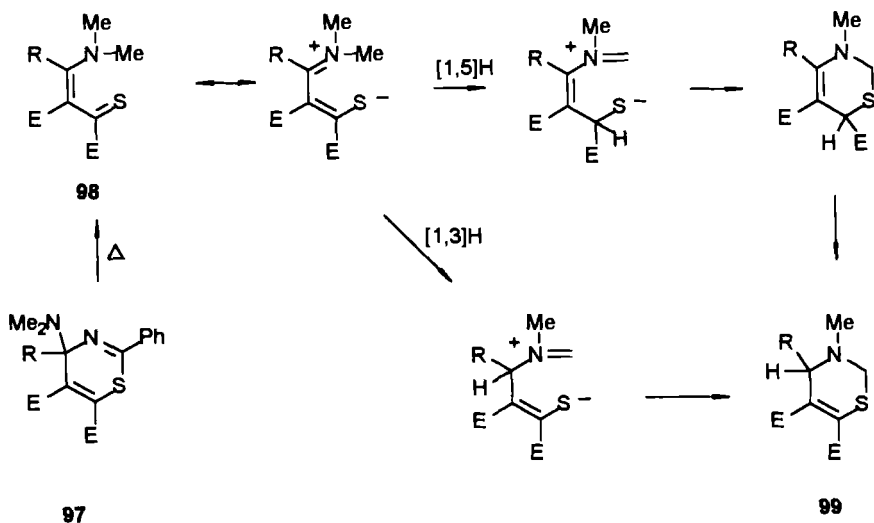
2-Thiocarbonylphenylpyrrolidines **93** analogous to the ketones reported above are versatile precursors for the formation of pyrrolidinobenzothiazines **94–96** (84T4309; 89RTC147). The starting materials are readily formed from the corresponding ketones with Lawesson's reagent and are rapidly transformed into the products during formation. However, while a variety of thiocarbonyl types undergo this reaction (unlike the ketones, which are limited to trifluoroacetyl derivatives), their regioselectivity is poor although their stereospecificity is high (Scheme 31). The greater anion-stabilizing capability of the sulfur accounts for the wide range of thiocarbonyls undergoing this process while the stereospecificity follows the same reasoning as that mentioned earlier for $C=C$ analogs. Thus the preferred conformation for H transfer has the R and R' groups transoid, and the cyclization of the dipolar species occurs on the same face as that from which the H migrated.

French workers (86SC79) noted that thermolysis of a 4H-1,3-thiazine **97** took place by way of an acyclic thionoamine **98** to give a 2H-thiazine **99**, the reaction proceeding via the *t*-amino effect (Scheme 32).



R and R'' = H or Me; R' = H, Me, CF₃, Ph 33-77%

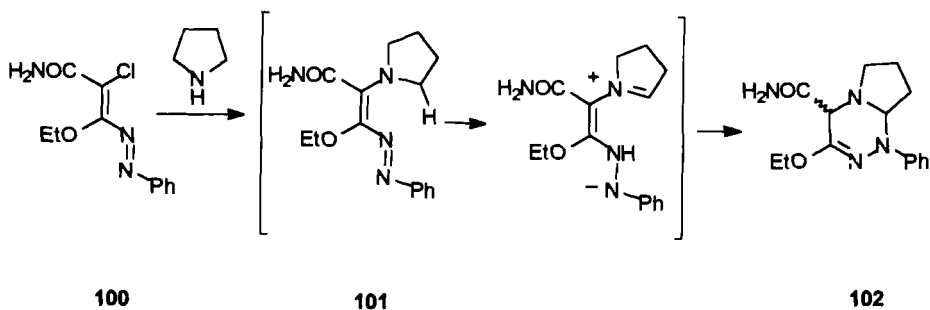
SCHEME 31



SCHEME 32

E. REACTIONS IN WHICH X=Y IS N=N

Azo compounds offer one of the rare cases in which both type 1 and type 2 products form from the same precursor (see our earlier review). An interesting example of a type 2 azocyclization is illustrated in Scheme 33. German workers (92BSB61) noted that the azoalkenyl chloride **100** reacted unexpectedly with pyrrolidine (unlike morpholine and other nucleophiles) to give a triazine **102** by way of the azoenamine **101**. This product is accounted for by the 1,5-H transfer and subsequent cyclization (Scheme 33).



SCHEME 33

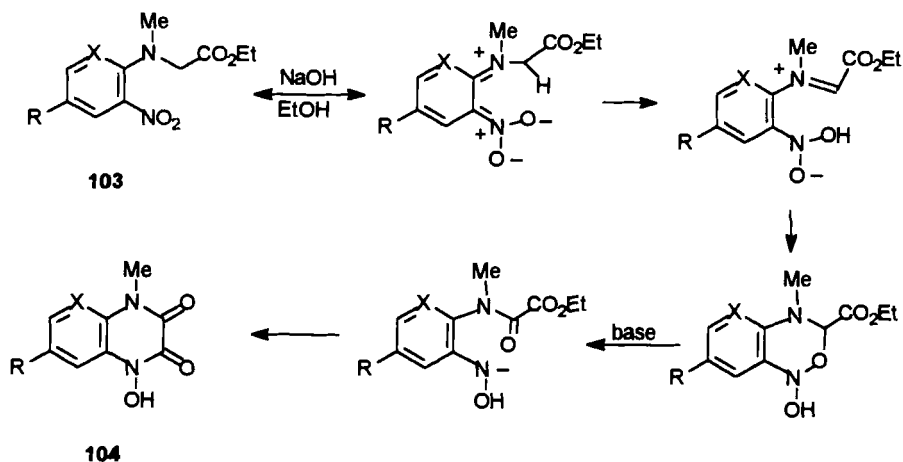
F. REACTIONS IN WHICH $X=Y$ IS $N=O$

The formation of an *N*-hydroxyquinoxaline-2,3-dione **104** from an (2-nitrophenyl)sarcosine **103** by the action of aqueous alkali could be accounted for by invoking a *t*-amino effect (Scheme 34) (87TL6363).

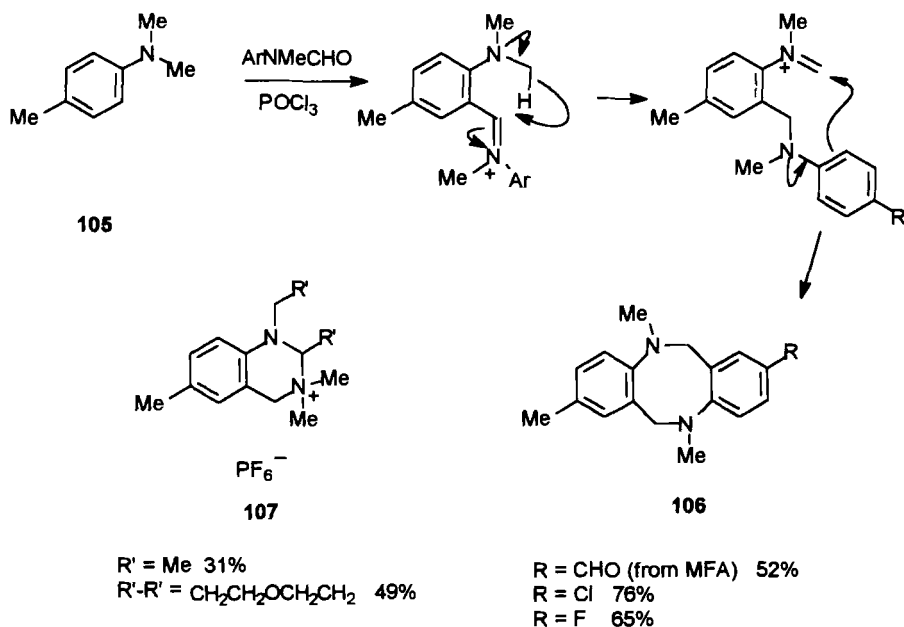
IV. Type 3 Reactions: Formation of Rings Containing More Than Six Members from *t*-Amino-Effect Reactions

This type of reaction is quite new and as yet undeveloped. The possibility that the dipolar intermediate involved in all *t*-amino-effect reactions discussed thus far reacts in other than the expected manner should be plausible given a suitable conjugated system. It is this type of possibility that allows extension of the *t*-amino effect to the formation of higher-membered rings.

The first example is shown in Scheme 35. Attempts to formylate *p*-substituted *t*-anilines resulting in dealkylation have already been mentioned (see Section II,B and Scheme 11). When such *t*-anilines as **105** are treated with *N*-methylformanilide in $POCl_3$ solution, for example, a diazocine **106** is formed (95CC1463)! When *N*-methylformanilide is used, *p*-formylation of the resultant diazocine also occurs to give **106**, $R = CHO$. However, when an aliphatic amide is utilized, the quinazolinium salts **107** are formed (which are probably the kinetic products in the diazocine formation). When such bulky formylamines as *N*-formyldiisopropylamine or -indoline are



SCHEME 34



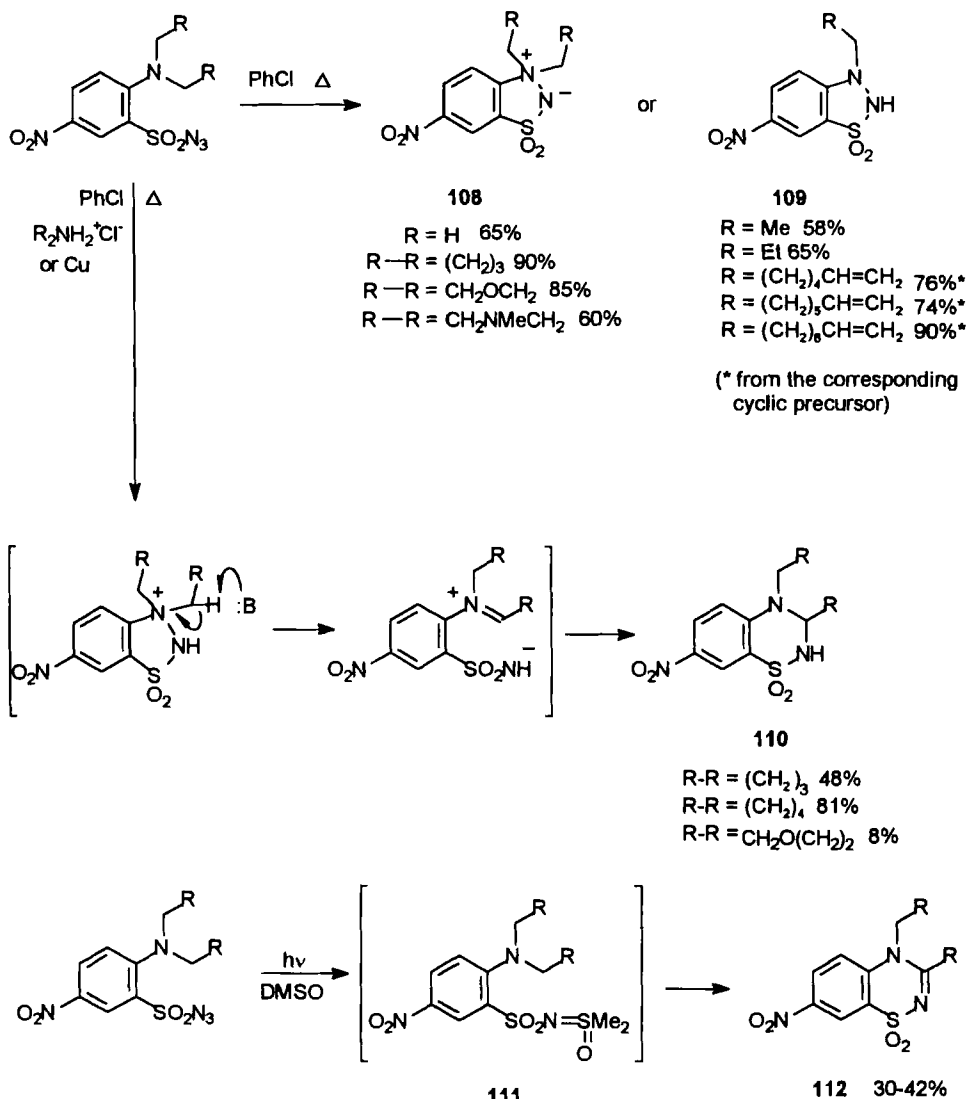
SCHEME 35

used, no "formylation" occurs; but with *N*-formyltetrahydroquinoline, normal formylation takes place. Clearly, this chemistry requires further work, but the reactivity of the Vilsmeier amide is sensitively dependent on the steric constraints. This chemistry is currently under active development.

V. Type 4 Reactions: Reaction of *ortho*-Substituents at the *t*-Amino Nitrogen

This group of reactions results in products derived from attack at the *t*-amino nitrogen, and a number of examples were presented in the previous review.

The thermolysis of *o*-azidosulfonyl-*t*-anilines resulted in nitrene formation and trapping of the nitrene by the adjacent amino nitrogen to give a zwitterionic thiadiazole dioxide **108** from the dimethyl- or 6-membered heterocyclic ring precursor. The ring-opened/dealkylated derivative **109** was formed from other dialkyl or ring systems (Scheme 36) [74 JCS(P1)2451]. The pyrrolidino azide was unique in giving no thiadiazole, but rather products derived from a sulfonylnitrene precursor, perhaps in



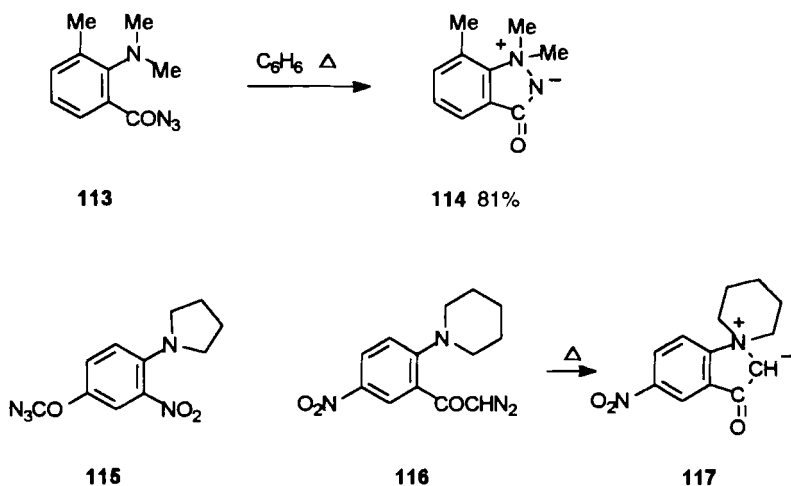
SCHEME 36

equilibrium with the unstable thiadiazolium ylide **108** $RR = (CH_2)_2$. These results are in total contrast to ring size effects in other *t*-amino effect reactions (*q.v.*). In the presence of catalytic amounts of amine salts or larger amounts of amine, the thiadiazine **110** was produced presumably by way of the ylide as shown. However, in the presence of copper, the thiadiazine **110** was also isolated, being formed more efficiently, and was also

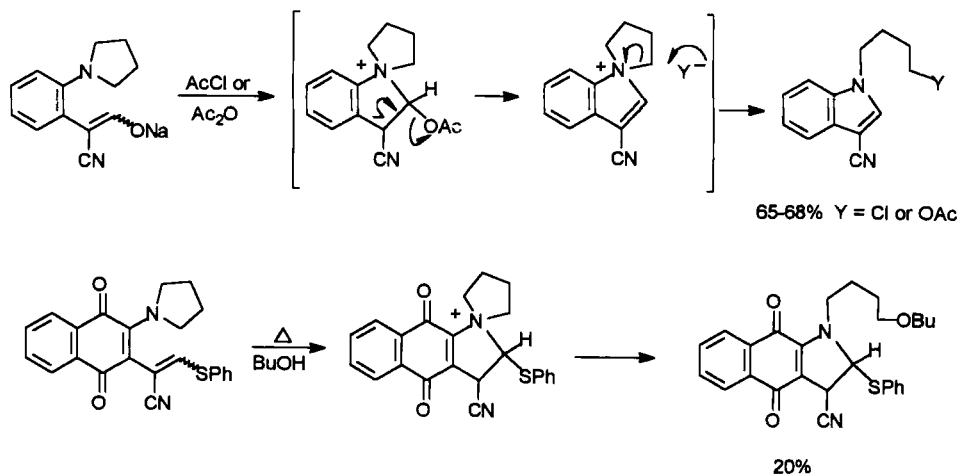
derived by similar treatment of the ylide. When the copper-catalyzed thermolyses were conducted in DMSO solution (known to trap sulfonylnitrenes as sulfoximides **111**), both the thiadiazine **110** and its dehydro derivative **112** were produced. The latter product was shown not to be an oxidation product, thereby supporting the idea that it derived from the sulfoximide as shown. Irradiation of the azides in DMSO also generated the thiadiazines **112**. Since the thiadiazole ylide **108** and the thiadiazine **110** were unchanged on irradiation, this was further support for the sulfoximide intermediate.

Abramovitch and co-workers (77JOC2920) independently showed that thermolysis of the 2-dimethylaminobenzenesulfonyl azide under slightly different conditions gave the same thiadiazole **108** together with minor products including the thiadiazole with a methyl group rearranged to the other nitrogen. They showed that this was a product of thermolysis of **108**.

When we examined the analogous benzoyl azides, we observed products of Curtius rearrangement only. However, recent work by Waldron and co-workers (95CC81) has shown that appropriate 2-dialkylaminobenzoyl azides **113**, which prove to be highly thermosensitive, do indeed give the indazole ylide **114** on warming, together with the products of Curtius rearrangement (Scheme 37). It seems evident that, in contrast to the reaction of the sulfonyl azides, this reaction involves concerted loss of nitrogen with either trapping by the *ortho* nitrogen or rearrangement, since acyl azides are known *not* to give nitrenes on thermolysis. To underline this concerted neighboring-group effect, when the 2-nitro-4-azidocarbonylphenylpyrrolidine **115** was thermolyzed, it normally decomposed to give Curtius products at $\sim 107^\circ\text{C}$ rather than at ambient temperature as its isomers do



SCHEME 37



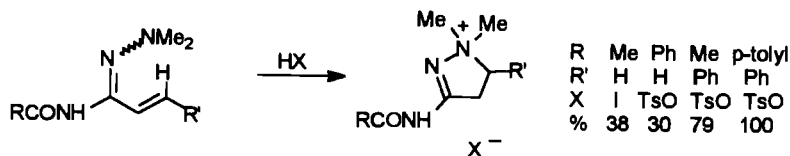
SCHEME 38

[74JCS(P1)2451]. Attempts to prepare the analogous diazomethane **116** gave a mixture of the required product together with the zwitterionic spiro-indolone **117** [74JCS(P1)2451].

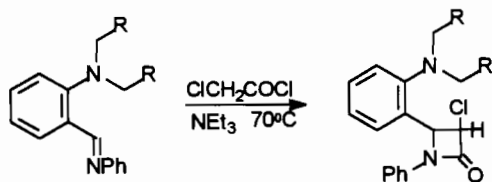
In our earlier review, we noted that when various types of *ortho*-substituted phenylpyrrolidines and -piperidines were treated with heat or an electrophile, cyclization with concomitant ring opening of the heteroring was observed. Some new cases involving the cyclization of *ortho*-C=C substituents to *t*-anilines have been noted by Verboom and Reinhoudt. Thus during their studies of mitomycin-analog synthesis, they observed that 2-cyanovinylphenylpyrrolidines react with acetylating agents to give 3-cyano-1-(ω -chloro- or acetoxybutyl)indoles (Scheme 38) (84TL2025; 85JOC3791). A similar process was noted when 2-pyrrolidino-3-cyanovinyl-naphthoquinone was heated in butanol to give a ω -butoxybutylpyrrolonaphthoquinone (Scheme 38) (88JOC2278).

An analogous reaction involves the action of HI or *p*-toluenesulfonic acid on a vinylamidrazone to give a pyrazolium salt (Scheme 39) (89JHC141).

The *ortho*-*t*-amino function can interfere in otherwise well documented reactions. Thus the β -lactams **119** from interaction of imines **118** and chloroacetyl chloride/triethylamine react further to give spiro derivatives **120** by



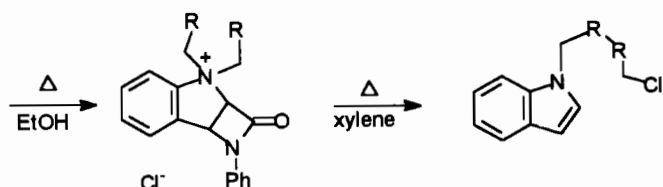
SCHEME 39



25-75%

118

119



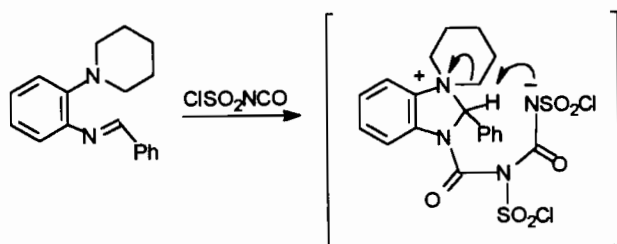
39-92%

85-95%

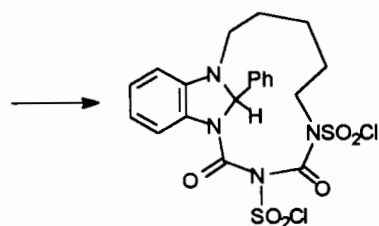
120

121

$\text{R} = \text{H}, \text{Me}; \text{R-R} = (\text{CH}_2)_2, (\text{CH}_2)_3, (\text{CH}_2)_4, \text{CH}_2\text{OCH}_2$



122



123

95%

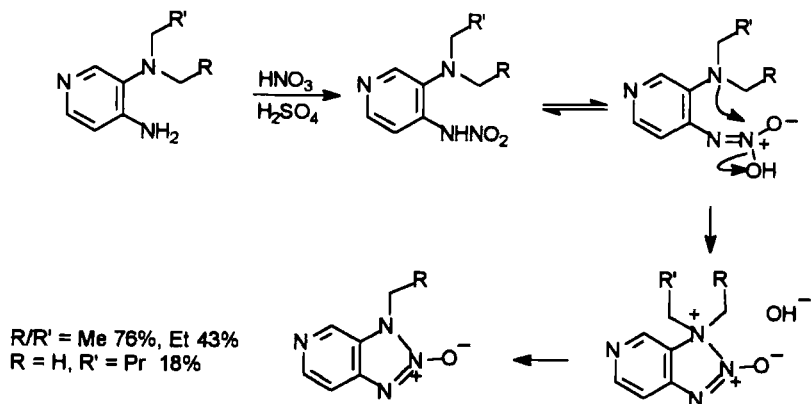
SCHEME 40

involvement of the *t*-amino function (Scheme 40) [76JCS(P1)1725]. By analogy with other reactions discussed above, the pyrrolidino- and dimethylaminoimines gave the spiro products directly. On thermolysis, these products undergo ring opening of the nitrogen heterocycle and loss of phenyl isocyanate to give *N*-(ω -chloroalkyl)indoles **121**. A variety of related acid chlorides and 2-*t*-aminophenyl imines have been similarly reacted. The benzaldehyde imine of *N*-(2-aminophenyl)piperidine **122** reacts with chlorosulfonyl isocyanate to give a macrocycle **123** in 95% yield, derived from involvement of the adjacent nitrogen (Scheme 40) [77JCS(P1)47].

The nitration of 4-amino-3-dialkylaminopyridines was discussed earlier (see Scheme 15). One of the products derives from a type 4 reaction, as shown in Scheme 41 [92H(34)1491], proceeding by formation of a nitramine which cyclizes onto the adjacent nitrogen without concomitant dealkylation.

VI. Type 5 Reactions: Trapping of Oxidatively Derived *ortho*-Iminium Salts

In this section, reactions are featured that involve the *ortho* trapping of an iminium ion generated oxidatively *without* the abstraction of H by the adjacent group. (In principle, this process could also involve an α -amino radical). Some years ago, we demonstrated that MnO_2 oxidation of *o*-substituted *t*-anilines can lead to intermediates that can be trapped by appropriate *ortho* nucleophiles [68JCS(C)1722; 69CI(L)443]. Thus *o*-amino- and *o*-carboxyphenyldialkylamines were cyclized to give

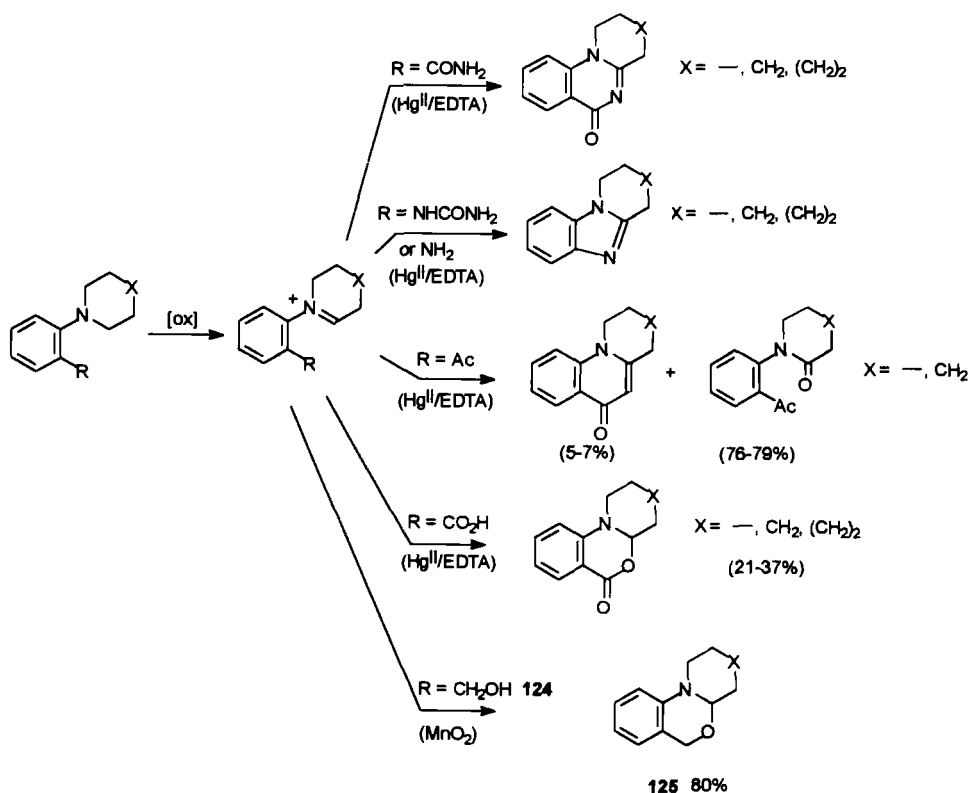


SCHEME 41

the corresponding benzimidazoles and benzoxazinones. Möhrle and co-workers [78AP(311)381, 78AP(311)586; 79AP(312)219; 81AP(314)524; 82AP(315)119, 82AP(315)339] have further exemplified this chemistry with a variety of examples as shown in Scheme 42. Kienzle (83TL2213) has shown that the *ortho*-hydroxycarbonyl derivative **124** gives the corresponding oxazinone **125** with MnO_2 (Scheme 42).

VII. Concluding Remarks

This review of necessity brings together disparate information not always recognized as part of the "*t*-amino effect" principle. Consequently, some examples in the literature may have been overlooked. I apologize to those whose work I have not acknowledged and would be glad to hear from them for the next update.



SCHEME 42

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63JCS4666
68JCS(C)1268
68JCS(C)1722
69CI(L)443
69JCS(C)70
72AHC(14)211
73JCS(P1)696
73TL4495
74JCS(P1)2451
74MI1
75KGS1360
76JCS(P1)1725
77H(6)1113
77H(6)1773
77JCS(D)872
77JCS(P1)47
77JOC2920
77JOC3317
78AP(311)381
78AP(311)586
78H(8)813
78H(9)1607
78JOC4472
78TL1351
79AP(312)219
79RTC251
81AP(314)524
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81JOC424
81T3525
82AP(315)119
82AP(315)339
82CC669
82JOC3339
82TL1217
83CC817
83JA4775
83TL2213
83TL3923
84JA1341
84JOC269
84TL2025
84TL4309
85JOC3791
85JOC3797
85SC1181
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Ring Contraction of Heterocycles by Sulfur Extrusion

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Germany*

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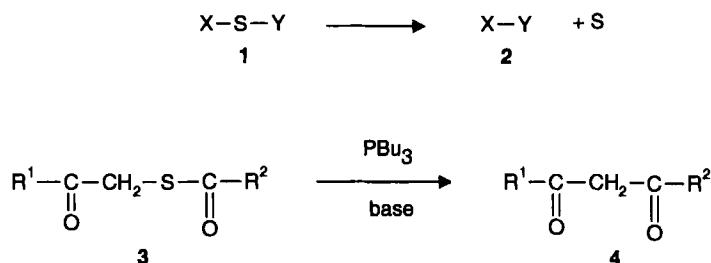
I. Introduction

Sulfur-containing moieties, such as SH, SR, SO, SO₂, SCl, SO₂R, or SO₃R, play an important role as powerful leaving groups in substitution and elimination reactions. Furthermore, the sulfur atom itself can be split off in so-called sulfur extrusion reactions, which may be represented in general form by the formation of compound **2** from **1** (90MI2), as shown in Scheme 1. The conversion of thioesters **3** into 1,3-diketones **4** is a specific example of this type of reaction (71HCA710; 90MI2).

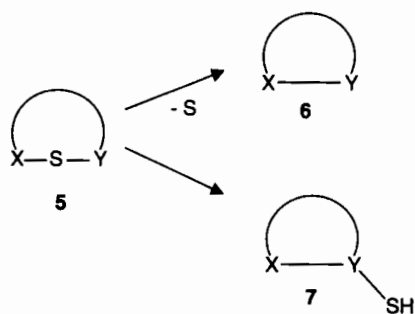
The present review deals with sulfur extrusions from heterocyclic compounds **5**, giving rise to ring-contracted cyclic products **6** (Scheme 2). In the course of such ring contractions, the sulfur atom sometimes remains connected to the final ring system (formation of **7**). This type of reaction is also considered to some extent in the following sections.

Although the generation of alkenes **9**, **11**, and **13** from oxathiolane **8** [72JCS(P1)305], from 1,3,4-thiadiazolines **10** [74JCS(P1)1794], or from episulfides **12** (85HOU1482; 90MI2, 90RCR405, 90UK705), respectively, as well as the transformation of thiophenes **14** into butanes **15** or butadienes **16** (88ACR387; 90MI1; 92CRV491; 94HOU186) represent examples of desulfurizations of heterocycles (Scheme 3), these sulfur extrusions are not included since open-chain products are obtained rather than cyclic compounds. The same applies to the cheletropic formation of butadienes **18** from 2,5-dihydrothiophenes **17** (71JA2344) (Scheme 3).

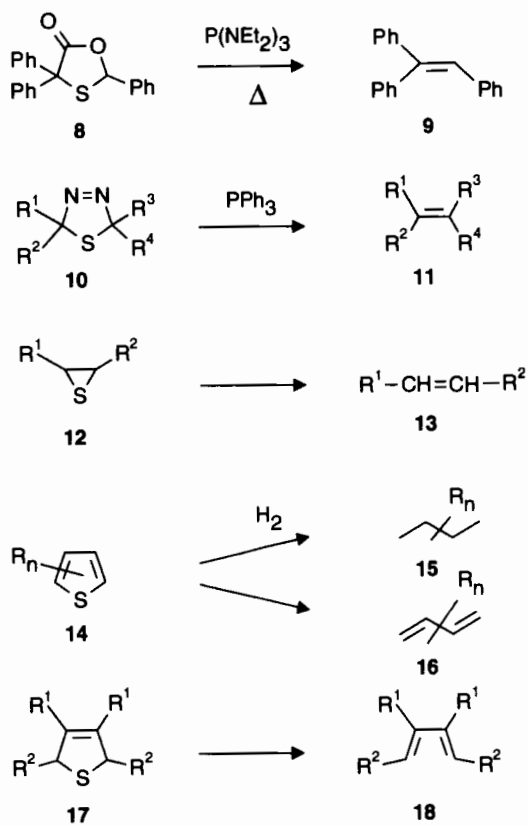
Various methods, such as thermolysis, photolysis, interaction with trivalent phosphorus compounds [e.g., PR₃, P(NR₂)₃, P(OR)₃] or bases, and reaction with nickel catalysts or oxidizing agents (e.g., H₂O₂, RCO₃H), are useful for the ring-contraction reaction of heterocycles by sulfur extrusion. In a number of cases, the reagent adds to the sulfur atom in a first reaction step (Scheme 4). Hence, instead of elemental sulfur, its derivatives are eliminated in the subsequent ring contraction, such as SO₂ in the presence



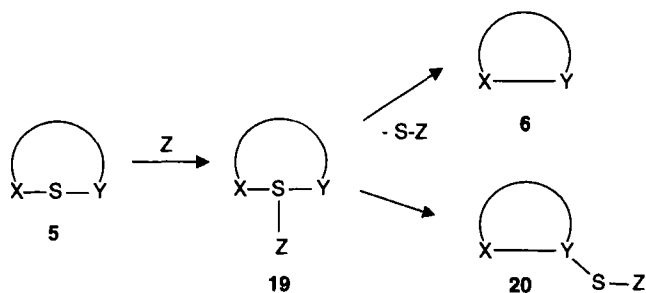
SCHEME 1



SCHEME 2



SCHEME 3

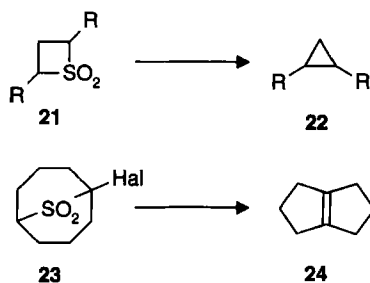


SCHEME 4

of oxidizing reagents, nickel sulfide in the presence of nickel complexes (79MI1), or $\text{S}=\text{PR}_3$ if trivalent phosphorus compounds PR_3 are used as desulfurizing agents. Alternatively, modified mercapto-substituted cyclic products **20** can be formed if the original $\text{S}-\text{Y}$ bond is retained, as in the methylation/Stevens rearrangement reaction sequence (Scheme 4). (See also Scheme 73 in Section VI.)

Reactions initiated by electrophilic or oxidative attack at the ring sulfur atom (Scheme 4) are considered in the present review only if intermediates **19**, such as *S*-oxides or *S*-dioxides, are not isolated but are transformed to the sulfur-free ring contraction product without prior isolation. Thus, sulfur dioxide extrusion from such isolated *S,S*-dioxides as thietane *S,S*-dioxide **21** or the Ramberg-Bäcklund reaction of α -halosulfonyl compounds (e.g., of **23**) (77OR1) (Scheme 5) are not included (for reviews on SO_2 extrusions from heterocycles, see 90MI1; 92MI1).

For further clarification we state that reactions such as the transformation of thiopyrylium salts **25** to pyridine or benzene derivatives **27** (71JHC301, 71T6083; 84MI1; 92HOU687) or the Dimroth rearrangement of thiopyrans



SCHEME 5

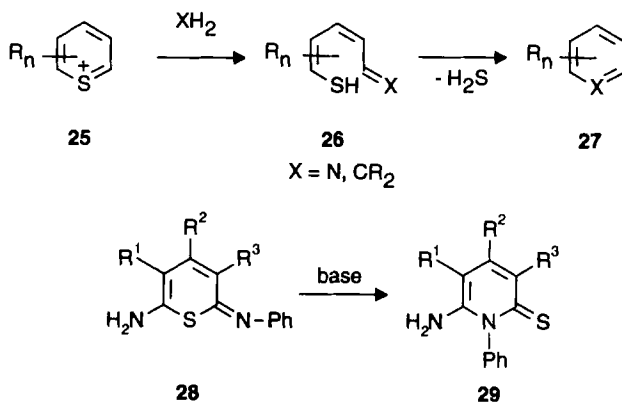
28 to pyridine-2-thiones **29** (73JPR679) (Scheme 6) are not considered, either. These transformations do not give ring-contracted products and do not fit into the class of extrusion reactions.

Furthermore, cycloaddition reactions of alkenes or alkynes **31** with thiophenes **30** ($X = C$) (84MI2; 94HOU186) or 1,3-thiazoles **30** ($X = N$) (84MI3; 94HOU1) are often followed by sulfur extrusion from the bicyclic cycloadducts **32**, affording benzenes or pyridines **33** ($X = C$ or N , respectively) (Scheme 7). These ring transformations are not considered in this review, since they do not involve ring contraction, but rather ring enlargement.

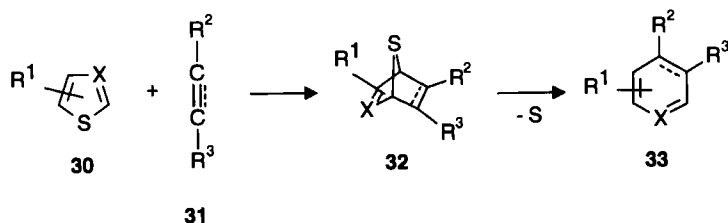
Within the limitations just mentioned, this review provides a comprehensive survey on ring contractions of heterocycles by sulfur extrusion—a review having a much wider scope than previous surveys in this field (61MI2; 67MI1; 87MI1; 88T6241; 90MI1, 90MI2).

The literature search for this review turned out to be complicated. Reaction data bases such as REACCS or ChemInformRX worked well but, as expected, could not give a complete survey of the relevant literature. Chemical Abstracts key words such as “sulfur extrusion” or “desulfurization” revealed numerous references dealing with industrial desulfurization of stock chemicals in addition to the citations of interest; nevertheless, these turned out to be incomplete (for similar problems in searching for sulfur extrusion reactions, see 90MI2).

Although reliable information on the mechanisms of ring contractions of heterocycles by sulfur extrusion are often difficult to obtain, some generally accepted concepts have been elaborated. Thus, fully conjugated seven-membered **34** and six-membered S-heterocycles **37** and **40** are antiaromatic



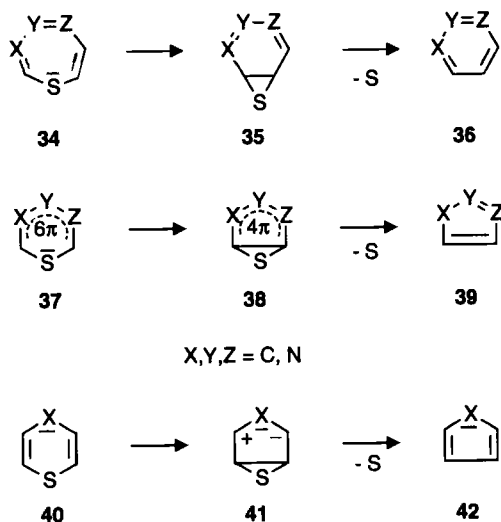
SCHEME 6



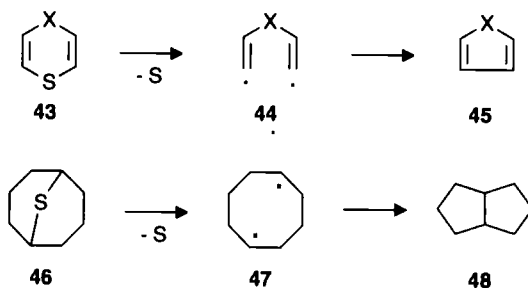
SCHEME 7

8π systems if planar. They are stabilized by disrotatory electrocyclic ring contraction (valence isomerization) to bicyclic thiiranes **35**, **38**, and **41** that ultimately extrude the sulfur atom [69CC1167; 72JOC552; 75AG603, 75AG(E)581; 79TL5003; 85TL3971] (Scheme 8). However, the elimination of singlet sulfur by a cheletropic reaction has been questioned for thermodynamic reasons. Elimination of concatenated sulfur species has been proposed instead (90MI2).

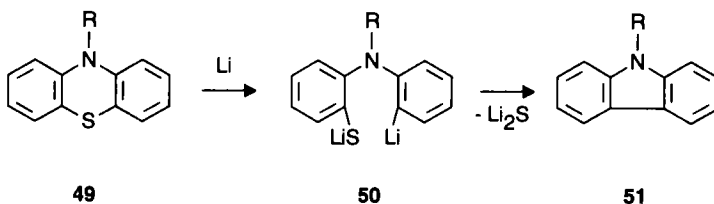
In sulfur extrusion reactions mediated by Raney nickel or nickel complexes (90MI1) or in reactions carried out under photolytic conditions (69JOC1233), biradical intermediates such as **44** and **47** are presumed to be present (Scheme 9). However, there is evidence that lithium-assisted desulfurization of phenothiazines **49** proceeds via open-chain intermediates **50** (58JA380) (Scheme 10).



SCHEME 8



SCHEME 9



SCHEME 10

II. Six-Membered Rings from Seven-Membered Rings

A. BENZENE DERIVATIVES FROM THIPIPINS

Most thiopins, especially if they are not highly substituted, readily extrude the sulfur atom under various conditions with formation of the corresponding benzene compounds. Extensive studies of the influence of substituents and annellation on the tendency to extrude the sulfur atom [for reviews, see 71IJS(B)267; 72MI1, 72MI2; 82RTC277; 83MI1] revealed that the stability of thiopins is increased by substituents, especially in the 2- and 7-position (by hampering the ring contraction), or by annellation of aromatic rings (83MI1). The instability of the thiopin system can be understood on the basis of its 8π -electron system and the resulting antiaromatic character—if it adopts a planar geometry—and is reflected in theoretical calculations (85JA6874).

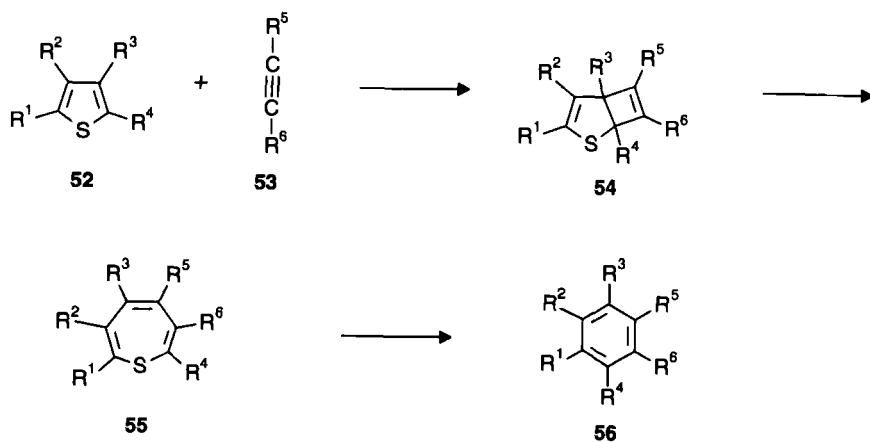
Thiopins sometimes undergo sulfur extrusion even during their preparation. Thus, thiopins **55** accessible from thiophenes **52** and alkynes **53** either slowly eliminate sulfur to form the corresponding benzene derivatives **56** (in some cases, even at -30°C) or they can be transformed to **56** by heating

(69TL2913; 71JOC3755; 72CC1233; 74T2093; 76TL4777; 78CJC1970; 79TL1529; 81JOC424; 82JOC977) (Scheme 11). Occasionally, thiopins do not lose the sulfur atom after the ring contraction, but rather open the thiirane ring to give thiophenol derivatives (79TL1529).

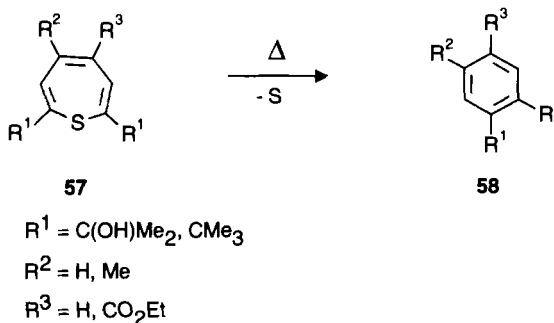
4-Ethoxycarbonyl-2,7-diisopropyl-5-methylthiepin **57** ($R^1 = i\text{-Pr}$, $R^2 = \text{Me}$, $R^3 = \text{CO}_2\text{Et}$) is not stable even at -50°C , but slowly extrudes sulfur (78CL723). However, the stability considerably increases if *tert*-butyl groups are present in the 2- and 7-positions. For example, the half-life of thiepin **57** ($R^1 = \text{CMe}_3$, $R^2 = \text{Me}$, $R^3 = \text{CO}_2\text{Et}$) in deuterated toluene at 131°C is 7.1 h. Regardless of their higher stability, thiopins **57** can be desulfurized by prolonged heating in a sealed tube (79JA5059; 80MI1) or in the presence of PPh_3 (70JA5263; 82TL3195) (Scheme 12).

The formation of thienothiophene **61** as a by-product of the thermolysis of thiepin **59** can be explained by the reaction of the starting material **59** with the extruded sulfur, which is in a highly reactive monomeric form. The initial step of this reaction is assumed to be a 1,2- and/or 1,6-addition (89PS243) (Scheme 13).

Benzo[*d*]thiepins with substituents in the 2- and 4-positions show various stability patterns. Thus, benzo[*d*]thiepin 2,4-dicarboxylic acid **62** ($R^1 = R^2 = \text{H}$, $R^3 = \text{OH}$) forms the corresponding naphthalene derivative **63** on standing in cold ethanol, under reflux in various solvents (53JA6332; 56CB2608; 58CB12), or by treating with nascent hydrogen at 40°C (58JOC104). Other derivatives of type **62** [$R^1, R^2 = \text{H}$ or $R^1/R^2 = -(\text{CH})_4-$, $R^3 = \text{OH}$, OMe , Ph] obtained from phthalic aldehydes and



SCHEME 11

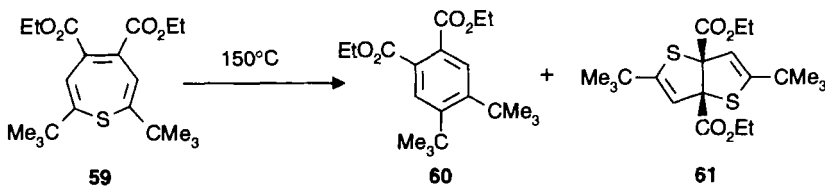


SCHEME 12

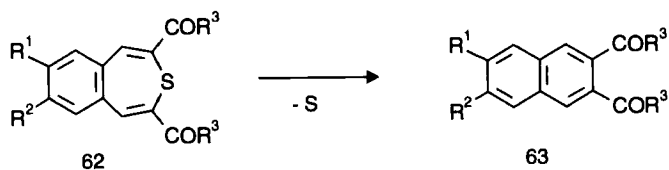
bis(carbonylmethyl) sulfides lose sulfur under the reaction conditions or can be desulfurized by dry heating (62JCS3262) (Scheme 14).

Unsubstituted benzo[b]thiepin **64** ($\text{R}^1\text{--R}^4 = \text{H}$) and the 2-chloro and 3-chloro derivatives slowly decompose at room temperature with the formation of the corresponding naphthalene and sulfur. *m*-Chloroperbenzoic acid accelerates this process, and benzo[b]thiepin *S,S*-dioxides are formed as by-products (73JOC3978). Substituents (Hal, Me, $\text{CH}=\text{O}$, Ph) in the thiepin moiety **64** afford higher stability. Half-lives were measured for various substituted benzo[b]thiepins and thiepins annellated to other heterocycles or naphthalene systems (73JOC3978; 75TL2697; 78JOC3379, 78TL3567; 83MI1). 5-Acetoxybenzo[b]thiepin rapidly extrudes sulfur in CCl_4 above 55°C , whereas temperatures above 70°C are necessary for the reaction of the 5-methoxy compound (85LA599; 88CB2147). The ring contraction of benzo[b]thiepins substituted by OR, Ph, and CN groups in the 3-, 4-, and 5-positions is readily achieved by heating in various solvents (75CB3596).

While the thermolysis of the 5-piperidino- and the 5-pyrrolidinobenzo[b]thiepin **66** in benzene results in desulfurization to naphthalenes **67**, the corresponding 5-hydroxy compound rearranges to the 1-hydroxy-4-mercaptanaphthalene **68** without loss of sulfur (72CC1232; 74T2431) (Scheme 15).

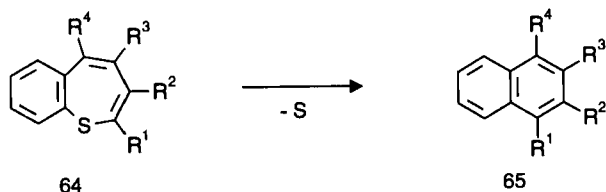


SCHEME 13



$\text{R}^1, \text{R}^2 = \text{H}$ or $\text{R}^1/\text{R}^2 = -(\text{CH})_4-$

$\text{R}^3 = \text{OH}, \text{OMe}, \text{Ph}$

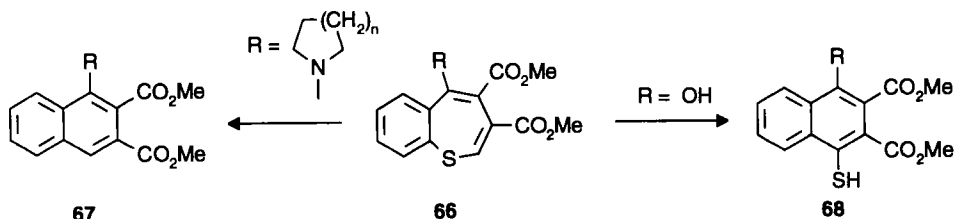


$\text{R}^1 - \text{R}^4 = \text{H}, \text{Hal}, \text{CH=O}, \text{Ph}, \text{OCOMe}, \text{OR}, \text{CN}$

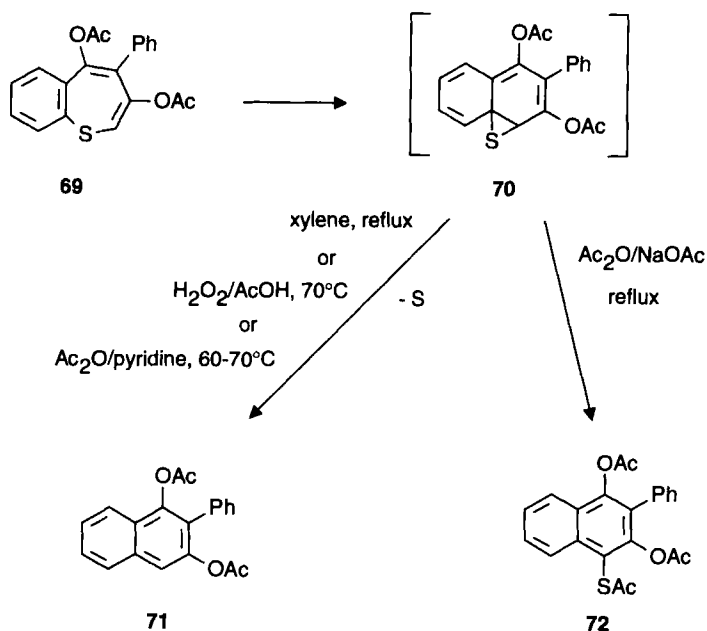
SCHEME 14

In some cases the type of thermolysis also depends on the reaction conditions (see the formation of **71** versus **72**) [67AG238, 67AG(E)255; 69CB2595] (Scheme 16). Furthermore, in the desulfurization reaction of 2-chlorobenzo[*b*]thiepin the formation of bis(α -naphthyl) disulfide as a by-product was observed (64JOC1092).

Benzo[*b*]thiepin structures are also assumed to be intermediates in sulfur extrusion reactions of cyclopropabenzothiopyrans (61JA4034; 69JOC56). Phenanthrenes **74** are formed when dibenzo[*b,f*]thiepins **73** are desulfurized under drastic conditions (57JCS3814) (Scheme 17).



SCHEME 15

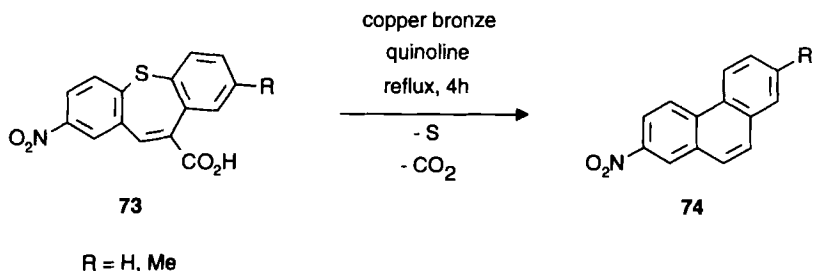


SCHEME 16

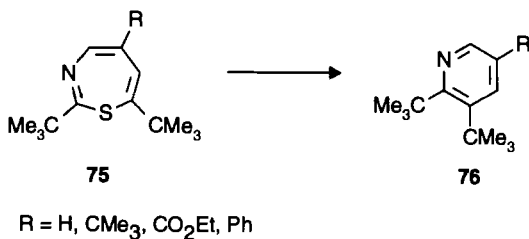
B. PYRIDINE DERIVATIVES FROM THIAZEPINES

1. From 1,3-Thiazepines

Owing to their instability, noncondensed 1,3-thiazepines (70ZC361) are difficult to synthesize. 2,7-Di-*tert*-butyl-1,3-thiazepines **75** are moderately stable and can easily be desulfurized to pyridines by thermolysis or by reacting with PPh_3 (89PS243) (Scheme 18).



SCHEME 17



SCHEME 18

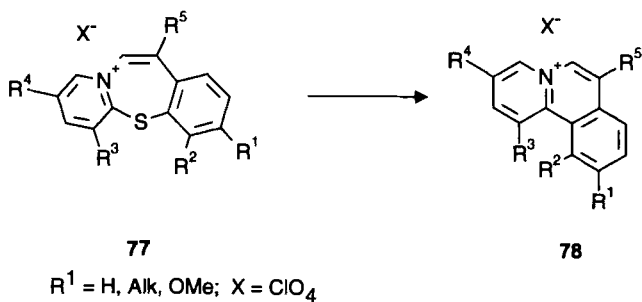
When bisannellated thiazepinium salts **77** are treated with H_2O_2 in acetic acid at elevated temperatures, pyrido[2,1-*a*]isoquinolinium salts **78** are formed in moderate yields [61CI(L)1797; 62JOC4475; 90JHC1073] (Scheme 19).

2. From 1,4-Thiazepines

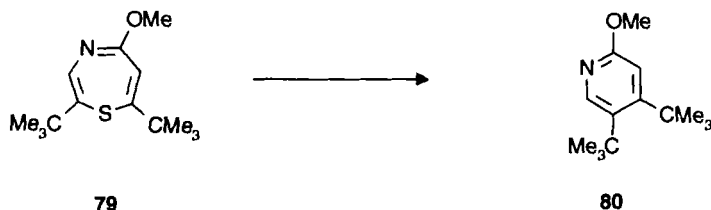
As with thiepins (see Section II,A), 1,4-thiazepines (70ZC361) are stabilized by bulky groups in the 2- and 7-positions. Thus, the 2,7-di-*tert*-butyl-1,4-thiazepine **79** is stable up to 130°C but is converted into the corresponding pyridine **80** by heating in a tube for 7 h at 110°C in the presence of PPh_3 [86AG639, 86AG(E)635] (Scheme 20).

5-Methoxybenzo[*f*]-1,4-thiazepine **81** is converted into the corresponding 1-methoxyisoquinoline **82** by refluxing in *n*-heptane for 14 h (88CB2147) (Scheme 21).

The isomeric benzo[*b*]-1,4-thiazepines **83** eliminate the sulfur atom with formation of quinolines **84** on heating in inert solvents ($\text{R}^1 = \text{OMe}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{H}$, Ph) [87CB2087, 87ZN(B)217], in isopropanol/morpholine ($\text{R}^1 = \text{SMe}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Ph}$) (70HCA1697), in the presence of *m*-



SCHEME 19



SCHEME 20

chloroperbenzoic acid ($R^1 = \text{OMe}$, $R^2 = R^3 = \text{H}$) [87ZN(B)217], or at room temperature ($R^1 = \text{H}$, $R^2 = \text{Ph}$, $R^3 = \text{CF}_3$) (91TL643) (Scheme 22).

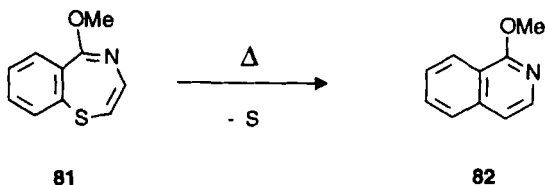
Benzo[*b*]-1,4-thiazepin-4-ones **85** ($X = \text{O}$) extrude sulfur to give quinolinones **86** ($X = \text{O}$). The same products, together with benzothiazoles, are formed by thermal H_2S elimination from the corresponding 2,3-dihydro compounds (86CB3109). The sulfur extrusion from benzo[*b*]-1,4-thiazepine-4-thiones **85** ($X = \text{S}$) to quinolinethiones **86** ($X = \text{S}$) requires catalysis by sodium alkoxides (70HCA1697) (Scheme 23).

Pyrido[2,3-*b*]-1,4-thiazepines were assumed to be unstable intermediates in the reaction of lithiated 2-chloro-3-cycloalkylidenaminopyridines with *O*-ethyl thiocarboxylates, yielding 1,5-naphthyridine derivatives after extrusion of sulfur (93S1227).

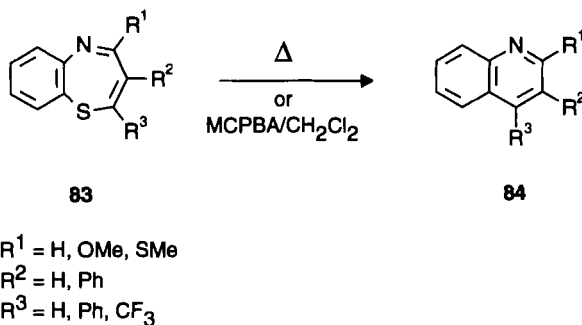
The desulfurization of dibenzo-annellated thiazepines **87** or higher annelated derivatives (58JCS1588) to phenanthridines **88** requires drastic reaction conditions (reflux in $\text{AcOH}/\text{H}_2\text{O}_2$ or thermolysis in the presence of copper bronze or cuprous cyanide or bromide) and can be accompanied by substitution reactions if bromo substituents are present on the benzo rings (54JCS3857; 57JCS3818; 58JCS1588; 59JCS885) (Scheme 24).

C. DIAZINE DERIVATIVES FROM THIADIAZEPINES

2,7-Dihydro-1,4,5-thiadiazepines **89** can be converted into pyridazines **90** by two methods: either by oxidation (NBS , Br_2 , SO_2Cl_2) and S-extrusion



SCHEME 21



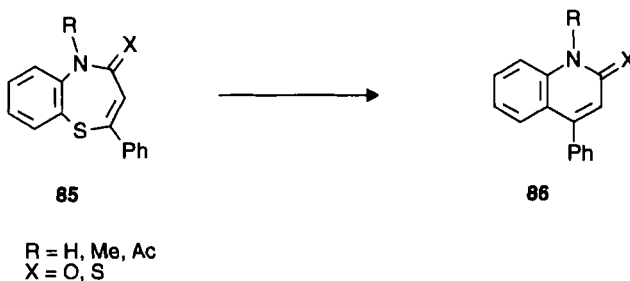
SCHEME 22

from the resulting intermediate 1,4,5-thiadiazepines (63JCS5496), or by thermal H_2S elimination in the absence of oxidizing agents (heating in 1,2-ethanediol or diethylene glycol). 4-Mercapto-4,5-dihydropyridazines are assumed to be intermediates in the latter cases (63JCS5496; 64JCS591; 89BCJ2608) (Scheme 25).

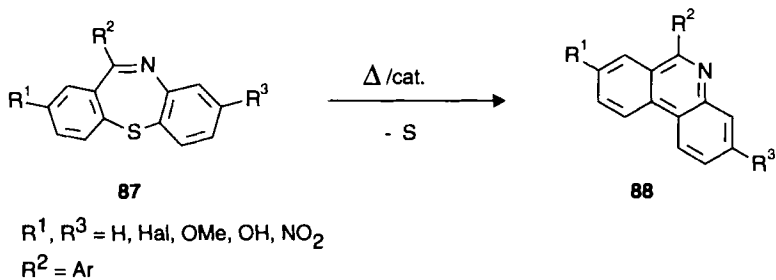
The 1,3,5-thiadiazepinone **91** extrudes sulfur when refluxed in toluene for 24 h (74JOC3763) (Scheme 26).

D. DITHIIN DERIVATIVES FROM TRITHIEPINS

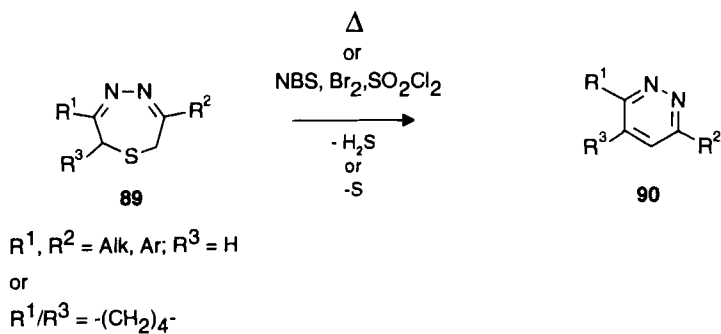
Oxidation of benzo[*e*]-1,2,3-trithiepane **93** gave only the ring-contracted product **94** rather than the expected benzo[*e*]-1,2,3-trithiepane 1,1-dioxide (88PS61) (Scheme 27). Pyrolysis of octafluoro-1,2,5-trithiepane **95** at 300°C yields the corresponding perfluorinated 1,4-dithiane (62JOC3995).



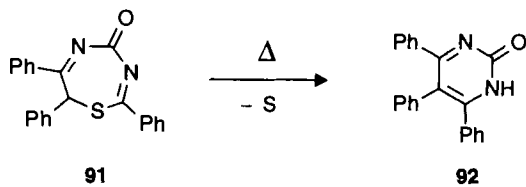
SCHEME 23



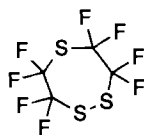
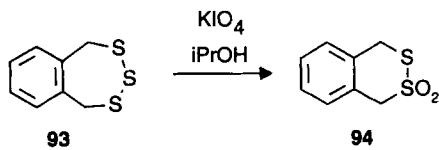
SCHEME 24



SCHEME 25



SCHEME 26

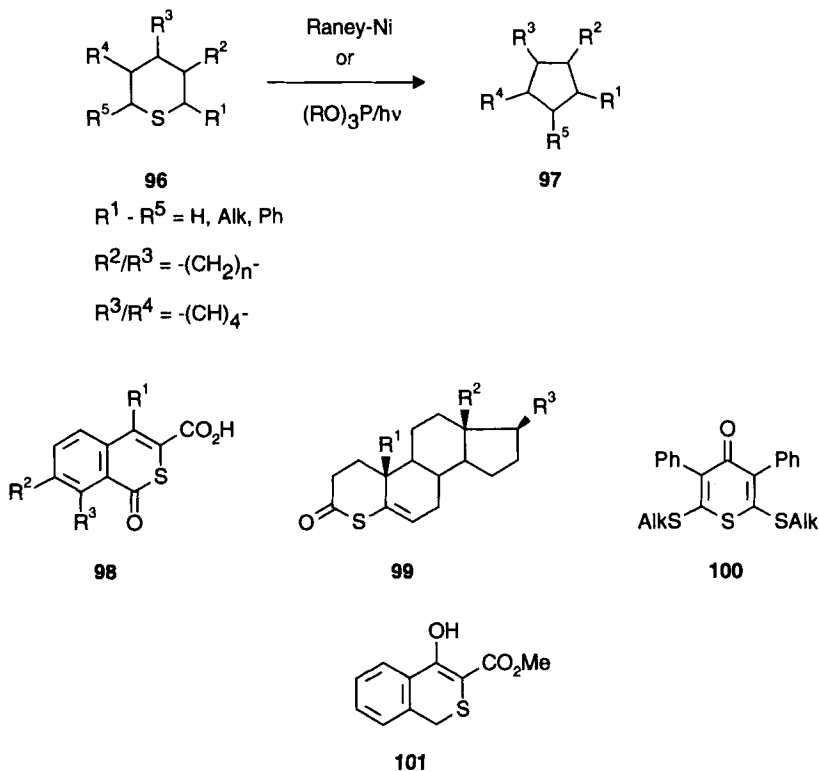


SCHEME 27

III. Five-Membered Rings from Six-Membered Rings

A. CYCLOPENTANE DERIVATIVES FROM THIOPYRANS

The formation of cyclopentanes or indanes from tetrahydrothiopyrans **96** or the corresponding benzo derivatives can be achieved in low yields by reaction with singlet carbon atoms (73JA1547), by treatment with Raney nickel [54LA(585)234; 72MI3] or with trialkyl phosphite under photochemical conditions (69JOC1233). In the latter case, predominantly alkenes are obtained. The analogous extrusion of sulfur in the presence of Raney nickel is possible from certain thiopyranones **98** (52JCS13), **99** (82CCC3148), and **100** [72JCS(P1)1203]. In the former two cases, the desulfurization is accompanied by the hydrogenation of the S—C=C double bonds. Ring contraction by sulfur extrusion was also observed when the benzothiopyran **101** was irradiated in methanolic solution (76JA5581) (Scheme 28).



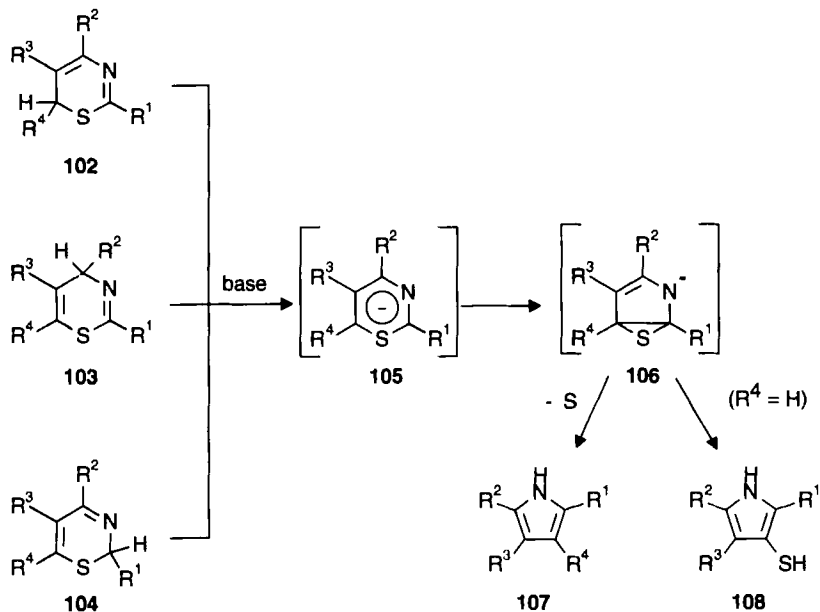
SCHEME 28

B. PYRROLE DERIVATIVES FROM THIAZINES

1. From 1,3-Thiazines

The desulfurization of 1,3-thiazines to pyrroles has a wide scope. Usually, a 1,3-thiazine **102**, **103**, or **104** is deprotonated by a base, such as RLi (75CB6; 85TL3971), KNH_2 (71JHC903), or an amine [85JCS(P1)1875; 91TL2225], affording an unstable antiaromatic 1,3-thiazine anion intermediate **105**, which contracts to an episulfide **106**. The latter either eliminates sulfur giving pyrrole **107** (71JHC903; 75CB6; 91TL2225) or rearranges to a 3-mercaptopyrrole **108** that can be further modified at the SH group [85JCS(P1)1875] (Scheme 29).

Starting 1,3-thiadiazines **102**, **103**, and **104** need not necessarily be isolated. They can be obtained by various methods, such as by cyclization [71JHC903; 85JCS(P1)1875; 91TL2225], by dimethylamine elimination from 4-dimethylamino-5,6-dihydro-(4*H*)-1,3-thiazines (91TL2225), by reduction of 1,3-thiazinium salts **109** with NaBH_4 (formation of mixtures of **102**–**104**) (75CB6), by electrochemical reduction of 1,3-thiazin-6-ones **110** [86MI1; 93JCR(S)282], or by addition of nucleophiles (morpholine or

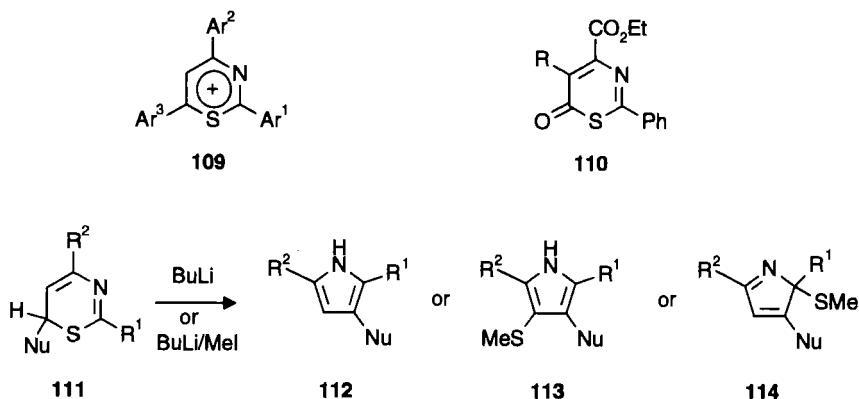


SCHEME 29

thiophenol) to 1,3-thiazinium salts (formation of **111**) (85TL3971). In addition to the expected desulfurized 3-amino- or 3-phenylthiopyrroles **112**, 2-methylmercapto-2*H*-pyrroles **114** or rearranged 3-morpholino- or 3-phenylthio-4-methylmercaptopyrroles **113** (85TL3971), which differ from the commonly observed 3-mercaptopyrroles **108**, can be obtained upon treatment of adducts **111** with BuLi and MeI (Scheme 30).

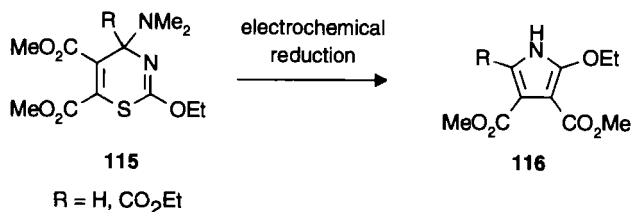
Unlike 6-amino-1,3-thiazines **111** (Nu = morpholino), 4-amino-1,3-thiazines **115** lose the amino group on electrochemical reductive desulfurization, yielding pyrroles **116** via 6*H*-1,3-thiazines even in the case of R = H (91TL2225; 92CJC14) (Scheme 31). The formation of **116** is assumed to proceed via elimination of amine and H₂S from intermediate dihydrothiazines.

The versatile desulfurization/rearrangement of 1,2-thiazolium salts **117** to pyrroles **119** is believed to proceed via intermediate 2*H*-1,3-thiazines **118** [93AG797, 93AG(E)712] (Scheme 32).



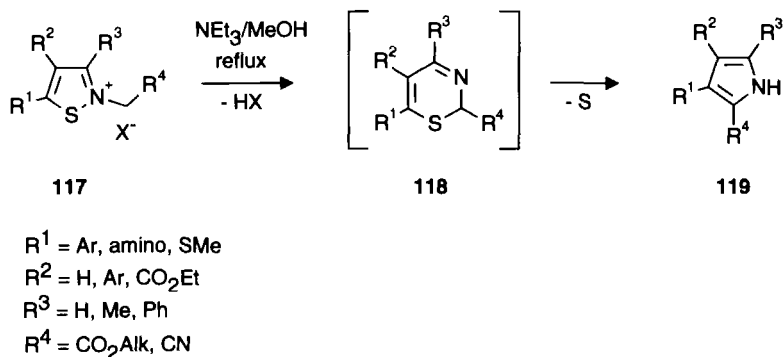
Nu = morpholino, PhS

SCHEME 30



R = H, CO₂Et

SCHEME 31



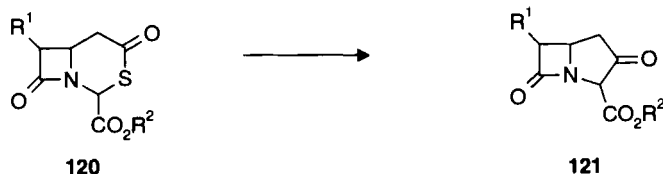
SCHEME 32

In the hydrogenated series the synthesis of carbapenem derivatives **121** by desulfurization with PPh_3 was reported (93EUP559533) (Scheme 33).

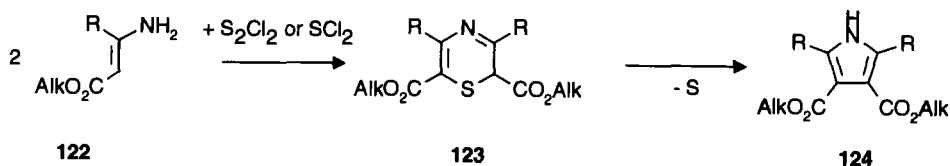
2. From 1,4-Thiazines

The addition of S_2Cl_2 or SCl_2 to 2 equivalents of aminocinnamates or aminoacrylates **122** affords 2*H*-1,4-thiazines **123**, which—depending on R —extrude sulfur under the reaction conditions ($\text{R} = \text{Ar}$) or can be isolated and desulfurized by treatment with NEt_3 to the corresponding pyrroles **124** ($\text{R} = \text{perfluoroalkyl}$) (84JOC4780; 85JHC1621) (Scheme 34).

The extrusion of sulfur from annellated 1,4-thiazines requires more drastic conditions. Thus, carbazole **126** and benzo-condensed derivatives can be prepared from the corresponding phenothiazines **125** by heating in the presence of freshly reduced copper (1886CB2240; 1887CB232; 1890CB2458; 30USP1772317), by heating in nitrobenzene or nitric acid/acetic acid (23CB1291), by reaction with lithium in THF [58CI(L)1367, 58JA380], or by reaction with a nickel complex derived from bis(1,5-cyclooctadiene)-nickel(0) and 2,2'-bipyridyl [77JOM(139)C51; 79M11; 86JA7763] (Scheme



SCHEME 33

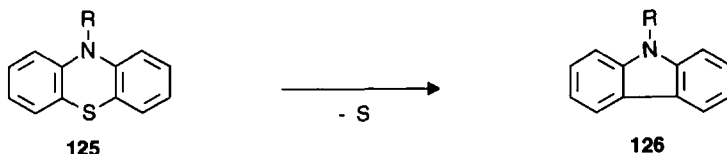


SCHEME 34

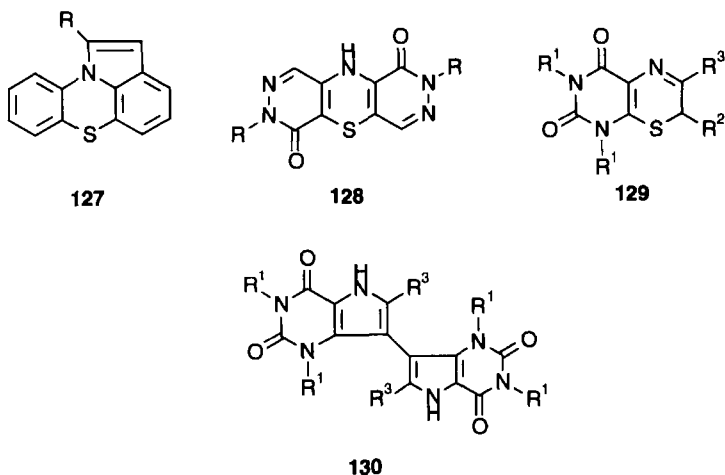
35). In the last examples, interaction of the nickel with the sulfur atom and formation of radical intermediates is discussed.

By the same method (85JHC1547) or by heating with K_2CO_3 in DMF (83H1507; 84CPB1423) or by refluxing in DMF, xylene, acetic acid, or methanol [71TL4185; 78AP(311)153; 81CC278], condensed heterocycles **127**, **128**, and **129**, respectively, are desulfurized to the corresponding condensed pyrroles. Starting material **129** ($R^2 = H$) can also afford dimerized desulfurization products **130** [78AP(311)153] (Scheme 36).

In contrast to an earlier report (87BCJ3713), some of the condensed 1,4-thiazines **131** are rather unstable and lose the thiazine sulfur atom during



SCHEME 35



SCHEME 36

their oxidative generation from the corresponding dihydro precursors (92BCJ1244). Dihydropyrido-1,4-thiazines **132** are extremely unstable at room temperature and are desulfurized even at low temperature (85H33) (Scheme 37).

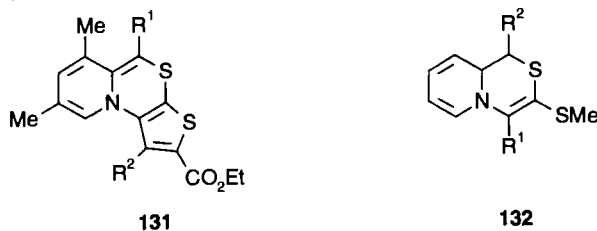
C. FURAN DERIVATIVES FROM OXATHIINS

Phenoxathiin **133** can be desulfurized by the bis(1,5-cyclooctadiene)-nickel(0)-2,2'-bipyridyl complex, affording dibenzofuran **134** [77JOM-(139)C51; 79MI1; 86JA7763] (Scheme 38). An analogous desulfurization in the presence of copper at 250°C (11BSF536) could not be verified in later investigations (36JA717; 40JA2606).

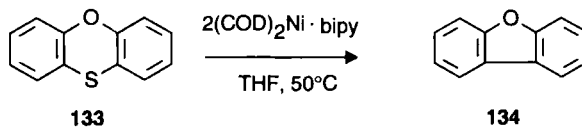
D. THIOPHENE DERIVATIVES FROM DITHIINS

1. From 1,2-Dithiins

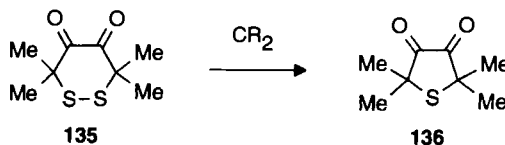
Sulfur extrusion from the cyclic six-membered disulfide **135** with formation of the dione **136** can be achieved by reaction with carbenes (85TL5187) (Scheme 39).



SCHEME 37



SCHEME 38



SCHEME 39

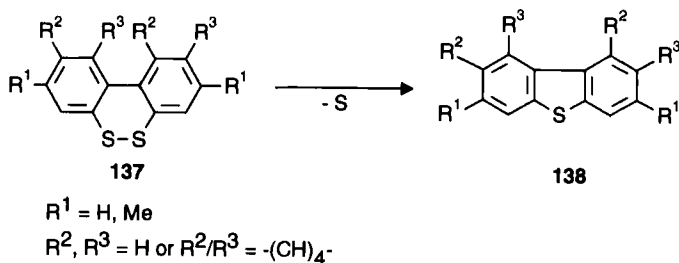
Thermal treatment of condensed 1,2-dithiins **137** with finely divided copper analogously affords dibenzothiophenes **138** (28JCS1141; 56JCS1665) (Scheme 40).

Naturally occurring thiarubrine A and thiarubrine B **139** (R^1, R^2 = alkynyl), as well as other 3,6-disubstituted 1,2-dithiins **139**, yield the corresponding thiophenes **140** on heating or irradiation [67AG685, 67AG(E)698; 85P356] (Scheme 41).

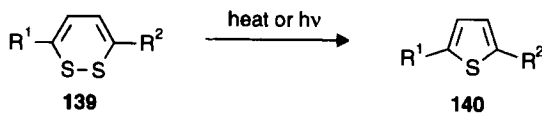
2. From 1,4-Dithiins

1,4-Dithiins **141** (for a review, see 61MI1) were often used as precursors for the synthesis of thiophenes by sulfur extrusion, which may be regarded as a 6π electrocyclic process (69CC1167). Whereas pure 1,4-dithiin is comparatively stable (53JA2065; 59JOC1819), substituted 1,4-dithiins, particularly 2,5-diaryl-substituted compounds, can be easily desulfurized to thiophenes **143** or **145** [$R^1 = R^3 = \text{Me}$, $R^2 = R^4 = \text{H}$: 59JA5993; $R^1 = R^2 = R^3 = R^4 = \text{CN}$: 62JA4746; $R^1 = R^2 = R^3 = R^4 = \text{CO}_2\text{R}$: 67CB1559; $R^1 = R^3 = \text{Ar}$, $R^2 = R^4 = \text{H}$: 54JA4960; 60JA4932; 64AJC353, 64TL3569; 79TL5003; $R^1 = R^2 = R^3 = R^4 = \text{Ar}$: 58LA(614)4; $R^1 = R^3 = \text{Ar}$, $R^2 = R^4 = \text{CO}_2\text{R}$: 61AG579; 64LA(679)118; $R^1 = R^3 = \text{Ar}$, $R^2 = R^4 = \text{H}$, Br: 56JA850; $R^1 = R^3 = \text{Ar}$, $R^2 = R^4 = \text{H}$, NO_2 : 55JA68; 56JA850] (Scheme 42).

Thermolysis [54JA4960; 55JA68; 58LA(614)4; 59JA5993; 60JA4932; 61AG579; 62JA4746; 64AJC353, 64LA(679)118, 64TL3569; 79TL5003],

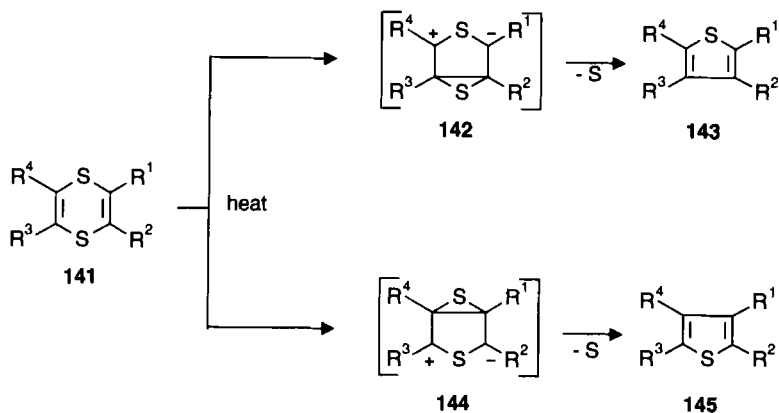


SCHEME 40



$R^1, R^2 = \text{H, alkynyl, (het)aryl}$

SCHEME 41

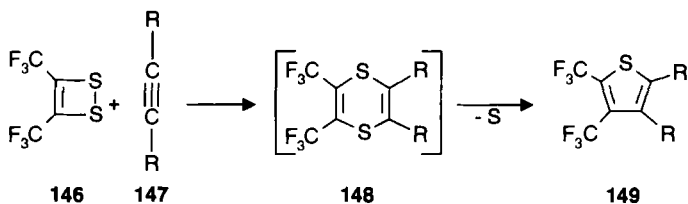


SCHEME 42

Raney nickel desulfurization (64AJC353), or intermediate oxidation of one sulfur atom [54JA4960; 55JA68; 56JA850; 58LA(614)4; 60JA4932] can be applied in these transformations. When unsymmetrically substituted dithiins **141** are desulfurized, two isomeric products, **143** and **145**, can be formed as mixtures (60JA4932; 85H1907). The preferred direction of the reaction can be explained by considering the different stability of the valence isomeric intermediates **142** and **144** (85H1907); e.g., if $R^1 = R^4 = \text{Ar}$ and $R^2 = R^3 = \text{H}$ or Alk, the zwitterionic intermediate **142** is more stabilized, thus giving a large excess of thiophenes **143** (product ratio **143**:**145** up to 15:1) (Scheme 42). Occasionally, dithienyl disulfides are obtained as by-products in the thermal desulfurization of 2,5-diaryl-1,4-dithiins (79TL5003).

The transformation of 1,2-dithiete **146** to thiophenes **149** is assumed to proceed via the desulfurization of 1,4-dithiins **148** (63USP3073844) (Scheme 43). Similarly, dihydrothiophenes are obtained if alkenes are used instead of alkynes (63USP3073844).

Desulfurization conditions applied to 1,4-dithiins may also cause reactions at other functional groups, such as formation of amides from carboxylic acids in the presence of SOCl_2 and aniline [64LA(679)118], introduction of a formyl group under Vilsmeier conditions (54JA4960), or the formation



SCHEME 43

of naphthothiophene **153** upon treatment of 2,5-diphenyl-1,4-dithiin **150** with dimethyl acetylenedicarboxylate **151** (77CL1149) (Scheme 44).

Condensed thiophenes **156–159** can be prepared from the corresponding 1,4-dithiins by heating in the presence of copper bronze (**156**: 37RTC627; **157**: 64JCS591), in the presence of Raney nickel (**156**: 64AJC366), by heating in a solvent or sulfuric acid (**158** [$R^1/R^2 = -(CH)_4-$]: 22CB2543; **159**: 63GEP1149934), by reaction with bis(1,5-cyclooctadiene)nickel(0)/2,2'-bipyridyl [**156**: 77JOM(139)C51; 79MI1; 86JA7763], or via the intermediate generation of the monosulfone by refluxing with 30% H_2O_2 in HOAc [**158** ($R^1 = R^2 = Me$): 69CB1739] (Scheme 45).

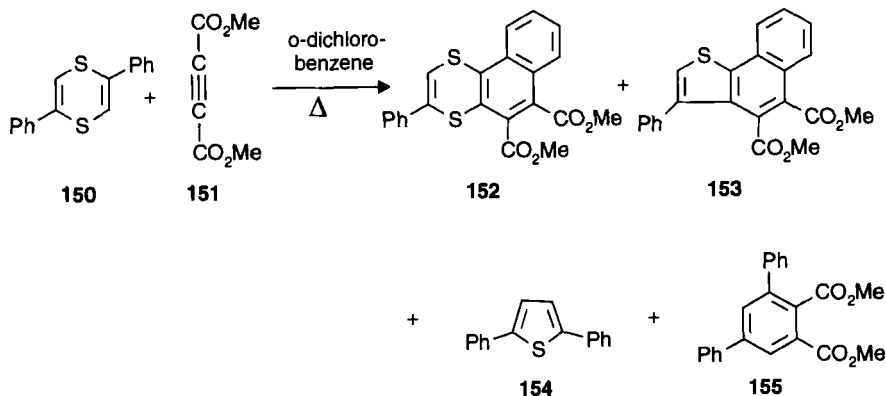
E. PYRAZOLE DERIVATIVES FROM THIADIAZINES

1. From 1,2,6-Thiadiazines

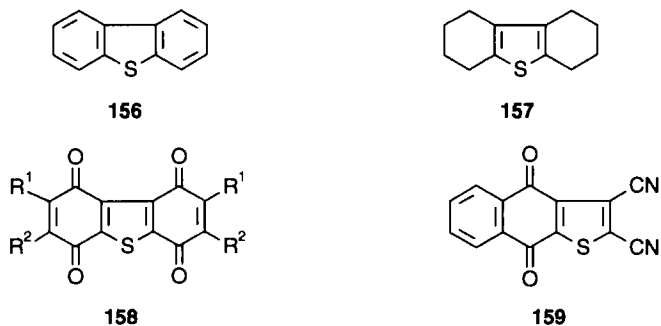
Like the 1,3,4-isomers (see the following section), 1,2,6-thiadiazines **161** afford pyrazoles **162** in desulfurization reactions. As a special feature, a N—N bond is formed in this ring contraction. It is not necessary to isolate the starting 1,2,6-thiadiazines **161**; trimethine derivatives **160** as corresponding precursors can also be directly transformed to pyrazoles **162** [81JCS(P1)1891] (Scheme 46).

2. From 1,3,4-Thiadiazines

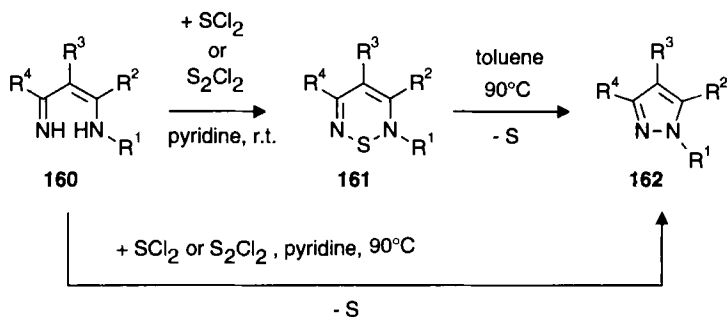
Ring-contraction reactions of 6*H*-1,3,4-thiadiazines **167** (or their tautomeric forms) were widely used for the preparation of pyrazoles **168** (Scheme 47 and Table I) (for reviews, see 69ZC361; 70MI1; 87MI1; 91KGS1443).



SCHEME 44



SCHEME 45

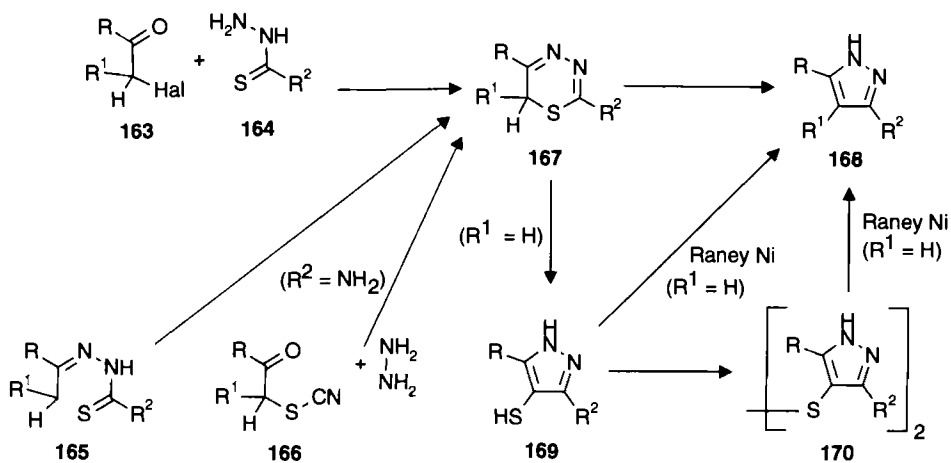


$\text{R}^1, \text{R}^4 = \text{Ar}, \text{c-hexyl}$

$\text{R}^2 = \text{Ar}$

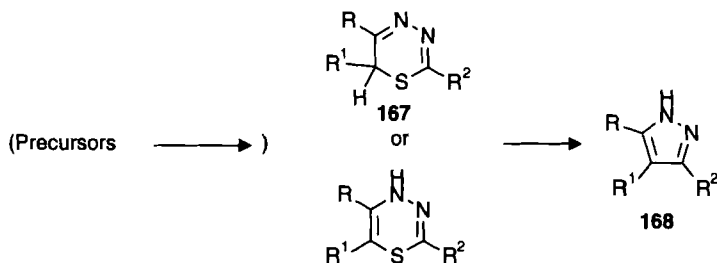
$\text{R}^3 = \text{H}, \text{Me}$

SCHEME 46



SCHEME 47

TABLE I
FORMATION OF PYRAZOLES FROM 1,3,4-THIADIAZINES



R = H, Alk, Ar, CO₂Et

R ¹	R ²	Reaction conditions	Remarks	Reference(s)
H	CH ₂ Ph	EtOH/PPh ₃ , reflux; or toluene/P(OEt) ₃ , reflux	A, B	77S485
	Ph	EtOH/PPh ₃ , reflux; or toluene/P(OEt) ₃ , reflux	A, B	77S485
	NR ₂	EtOH/PPh ₃ , reflux; or toluene/P(OEt) ₃ , reflux	A; B or C	77S485
		Ac ₂ O, reflux	A, D	70LA(741)45
		HOAc, reflux	A	70LA(741)45
		<i>hν</i>	A	93KGS565
		benzene/BuLi, r.t.	A, C	82ZC137
		THF/BuLi or benzene/ BuLi, r.t.	A	75TL33
		LDA, -110°C	A, B, C	75TL33
	SAlk	EtOH/PPh ₃ , reflux; or toluene/P(OEt) ₃ , reflux	A, B, C	77S485
Alk		HOAc, reflux	A, D	59CB2593
		THF/BuLi or benzene/ BuLi, r.t.	A	75TL33
	CH ₂ Ph	HOAc, reflux	A	76JPR(318)971
	Ph	EtOH/HCl, reflux	A	76JPR(318)971
	NR ₂	HOAc/reflux	A	77ZC218; 78ZC65
		HCl, reflux	A, F	78ZC65
		180°C/15–20 mm	A	74JAP(K)74/100080
Ar	SAlk	<i>p</i> -Me—C ₆ H ₄ —SO ₃ H, reflux	A	75JAP(K)75/130760
	CH ₂ Ph	HOAc, reflux; or EtOH, reflux	A, E	76JPR(318)971
	Ph	EtOH, reflux	E	76JPR(318)971
		xylene, reflux	A	60AK195

TABLE I (Continued)

R ¹	R ²	Reaction conditions	Remarks	Reference(s)
Ac CO ₂ Et	NR ₂	EtOH/HCl, r.t.	E, G	62ACS(A)2395
		EtOH/NaOEt, reflux or r.t.	A, H	77S196
		HOAc, reflux	A	70LA(741)45; 77ZC218; 78CCC1227, 78ZC65
		HCl, reflux	A, F	78ZC65
		benzene/BuLi, r.t.	A	82ZC137
		THF/BuLi, -80°C	A	75TL33
	SAlk	HOAc or toluene, reflux	A	59CB2593; 60AK195
		EtOH, HCl, r.t.	E, G	62ACS(A)2395
	NR ₂	EtOH, reflux	E	70LA(741)45
		CH ₂ Ph	EtOH, reflux	76JPR(318)971
	Ph	EtOH/HCl, r.t.	E	62ACS(A)2395
		EtOH/NaOH, r.t.	E	56AK523
	NR ₂	EtOH, r.t.	E	86CCC1692; 92CCC656
		EtOH, r.t. or reflux	E	70LA(741)45
		EtOH or EtOH/HCl, reflux	E	65CB259; 76JMC262
		EtOH/HCl, reflux	A	56CB1652
	NHNR ₂	EtOH/HCl, reflux	E	56CB2550
	SH	EtOH/NaOEt, r.t.	A, E	56AK523, 56MI1;
	SAlk			59CB2593

Remarks:

A, 1,3,4-Thiadiazine as starting material.

B, Formation of 4-mercaptopyrazole **169** as by-product.C, Formation of disulfide **170** from the 4-mercaptopyrazole **169** as side reaction.D, Formation of 4-mercaptopyrazole **169**.

E, 1,3,4-Thiadiazine generated in the course of the reaction; not isolated or not isolable.

F, Dealkylation of the amino group.

G, Prepared from dihydro-5-hydroxy-1,3,4-thiadiazine.

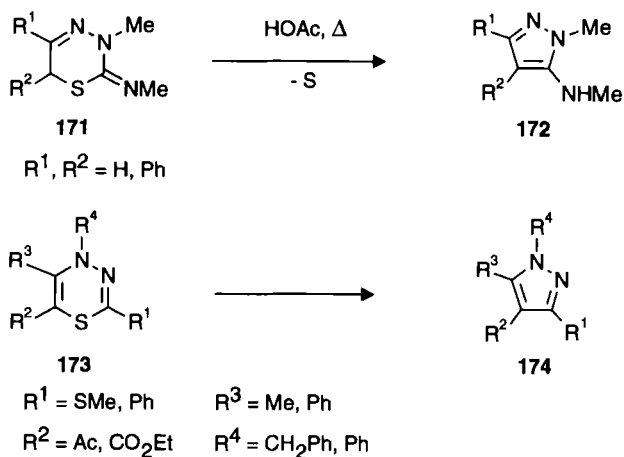
H, Sulfur isolated as thiosulfate.

Starting thiadiazines **167** can be prepared in various ways, such as from α -halocarbonyl compounds **163** and thiohydrazide units **164** (thiohydrazides, thiosemicarbazides, or thiocarbohydrazides), by oxidative ring closure of thioacylhydrazone derivatives **165** (56AK523), or by the reaction of α -thiocyanato carbonyl compounds **166** with hydrazine (69ZC361). In many cases, it is not necessary to isolate the 1,3,4-thiadiazines **167**. Depending on both the kind of substituents on the 1,3,4-thiadiazines **167** and the reaction conditions, the sulfur atom is either extruded from the ring system or is retained in the pyrazole ring as a 4-mercapto substituent (formation of **169**). Because of the great variability of starting components and reaction

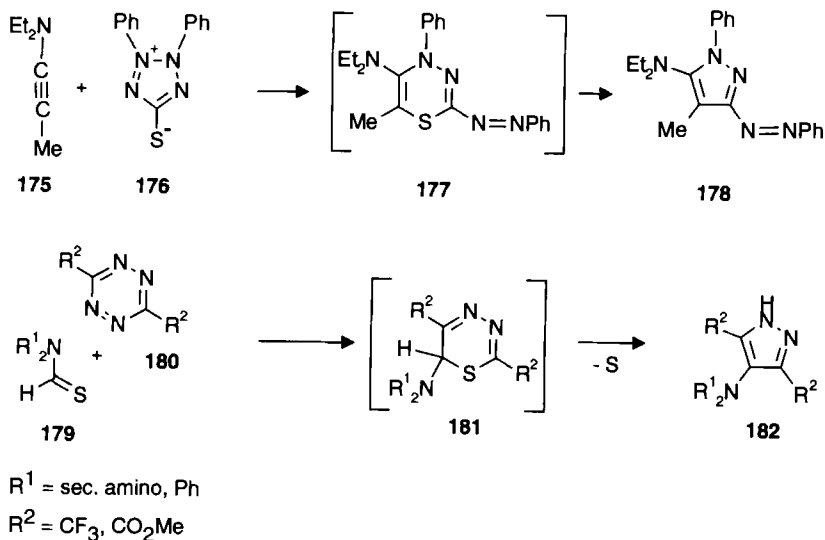
conditions, the scope of this type of reaction is wide. An overview is given in Table I.

The tendency of 1,3,4-thiadiazines to form pyrazoles is strongly influenced by substituents R^2 and R^1 in the 2- and, especially, in the 6-position, respectively (see Table I). Thus, ring contraction is facilitated by 6-ethoxycarbonyl, 6-acetyl, or 6-aryl groups (69ZC361; 70MI1) and can usually be accomplished by heating, for example, in EtOH, HOAc, EtOH/HCl, or EtOH/NaOEt (Table I). 1,3,4-Thiadiazines **167**, lacking a substituent in the 6-position ($R^1 = H$), usually require more drastic reaction conditions, such as refluxing in acetic anhydride, EtOH/ PPh_3 , or toluene/ $P(OEt)_3$ or reaction with BuLi. In these cases, the sulfur atom is usually not extruded but is, completely or to some lesser extent, retained in the molecule as a mercapto group, which may undergo further consecutive reactions such as acetylation [59CB2593; 70LA(741)45] or disulfide formation [59CB2593; 70LA(741)45; 75TL33; 77S485]. Thus, when heated with PPh_3 or $P(OEt)_3$ in ethanol or toluene, a number of 2-substituted 5-phenyl-6H-1,3,4-thiadiazines **167** ($R = Ph$, $R^1 = H$) yield the sulfur-free pyrazoles **168** or the corresponding 4-mercaptopyrazoles **169**, which may be spontaneously oxidized to the corresponding bispyrazole disulfides **170**. Compounds **169** and **170** can be desulfurized to **168** ($R^1 = H$) by Raney nickel in ethanol, thus affording the same pyrazoles as those obtained in the direct desulfurization route (77S485) (see Scheme 47).

Formation of N-substituted pyrazoles **172** (77ZC173) and **174** [56AK523; 62ACS(A)2395] is possible, starting from the corresponding N-substituted 1,3,4-thiadiazines such as **171** or **173** or their precursors (Scheme 48).



SCHEME 48



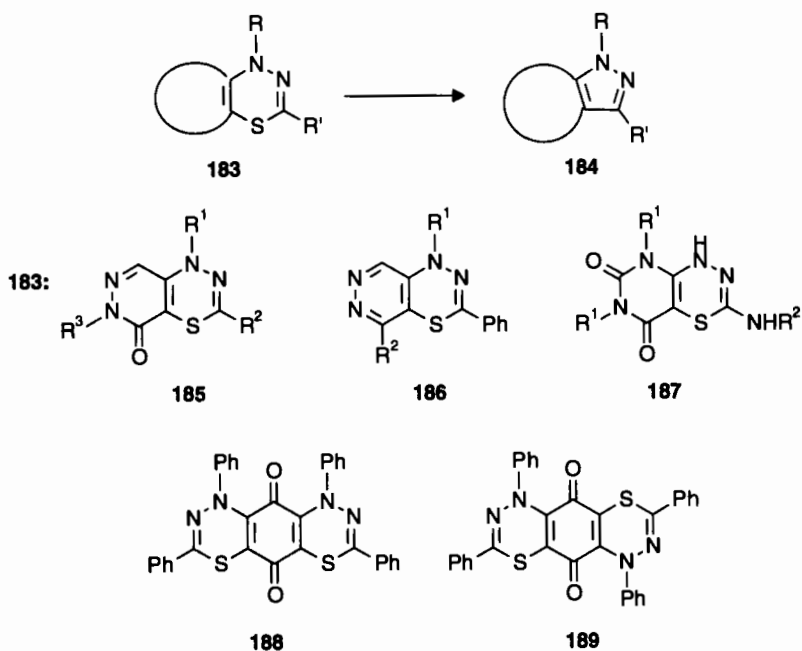
SCHEME 49

1,3,4-Thiadiazines **177** (74CC639) and **181** [84AG885, 84AG(E)890] are assumed to be intermediates in the transformation of dehydrodithi-zone **176** to phenylazopyrazole **178** and of the thioformamides **179** to 4-aminopyrazoles **182**, respectively (Scheme 49).

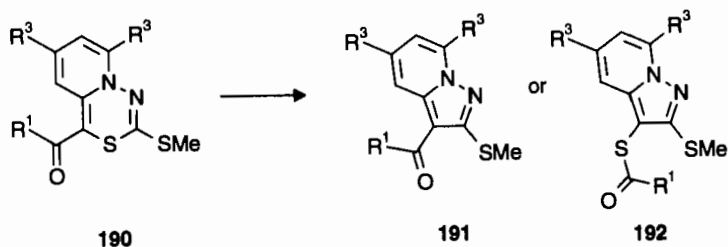
The ring contraction reaction of 1,3,4-thiadiazines can also be employed for the synthesis of annellated pyrazoles. Again, the corresponding condensed 1,3,4-thiadiazines are not necessarily the starting materials but can also be intermediates in the course of a reaction sequence. The ring contraction of *[e]*-annellated 1,3,4-thiadiazines **183** such as **185** (84CPB4437, 84H479; 85JHC161), **186** (84CPB4437), **187** (79CPB1328, 79CPB1965, 79MI2), and **188** or **189** (80JOC3677) can be achieved by melting, by heating in a solvent, by heating under basic conditions, or during their preparation (Scheme 50).

Depending on the substituent R^1 , transient pyrido[1,2-*d*]-1,3,4-thiadiazines **190** can give either desulfurized or rearranged pyrazolopyridines **191** or **192**, respectively, at room temperature (84H2237) (Scheme 51).

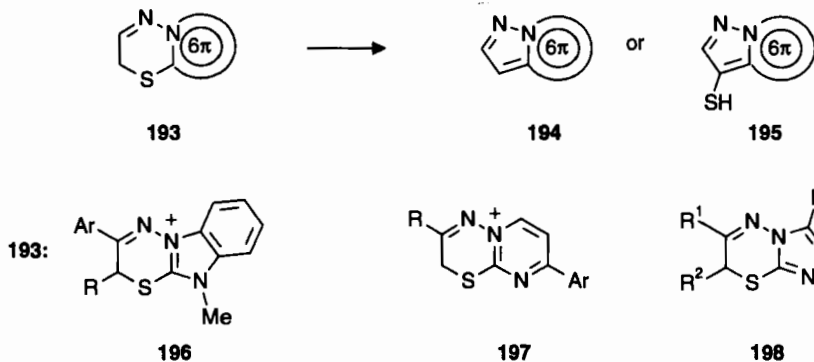
Similarly, in the *[b]*-annellated series **193** benzimidazothiadiazinium salts **196** (92KGS1698) afford condensed pyrazoles of type **194** or mercapto-substituted products **195**, depending on the reaction conditions. The latter type of rearranged mercaptopyrazoles **195** is exclusively formed by heating pyrimidothiazinium salts **197** (90JPR470) in DMF/ NEt_3 . However, triazolothiadiazines **198** [88JAP(K)88/101386, 88JAP(K)88/101387; 89JAP(K)89/



SCHEME 50



SCHEME 51



SCHEME 52

403186; 90JAP(K)90/101077; 91USP5055586] extrude sulfur upon heating in acetic anhydride or EtOH/TEA with formation of compounds of type **194** (Scheme 52).

F. IMIDAZOLE DERIVATIVES FROM THIADIAZINES

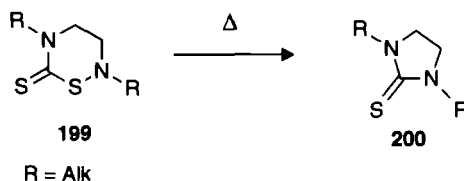
1. From 1,2,5-Thiadiazines

Desulfurizations of 1,2,5-thiadiazines are rare. Tetrahydro-1,2,5-thiadiazines **199** lose the sulfur atom by gentle heating without solvent, affording imidazolidine-2-thiones **200** (49JOC946) (Scheme 53).

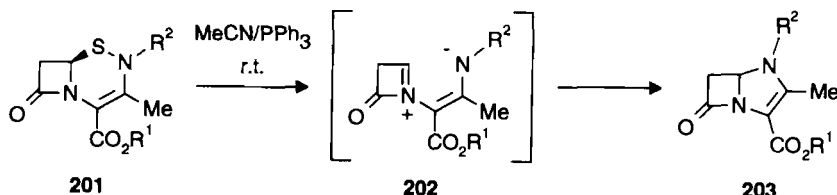
In the condensed series, 2-aza-1-thiacephem **201** can be desulfurized by triphenylphosphine in acetonitrile at room temperature with formation of azapenems **203**. The low order or absence of optical activity in the products is explained by an open-chain zwitterionic intermediate **202** (81CC1269) (Scheme 54).

2. From 1,3,5-Thiadiazines

Imidazoles **206** are formed in high yields when 1,3,5-thiadiazines **204** are treated with catalytic amounts of NEt_3 ($\text{R} = \text{Ar}$) or with potassium *tert*-butoxide ($\text{R} = \text{H}, \text{Me}$) at room temperature in an inert solvent. The appear-



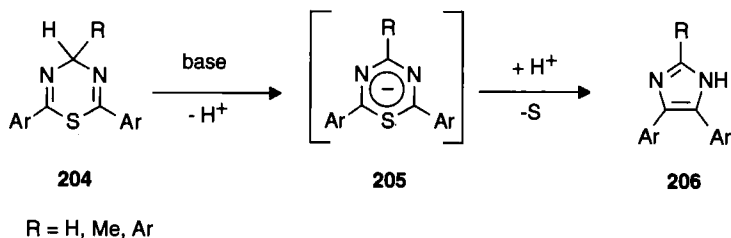
SCHEME 53



$\text{R}^1 = p\text{-NO}_2\text{-benzyl}$

$\text{R}^2 = \text{Et}, \text{Ph}$

SCHEME 54



SCHEME 55

ance of the highly reactive 8π -electron anion **205** was supported by kinetic measurements [75S167; 77JCS(P2)939] (Scheme 55).

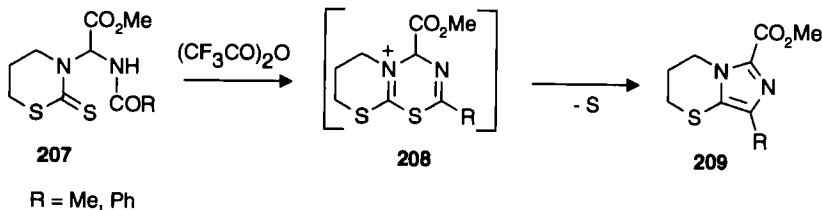
The formation of imidazole **209** from **207** is believed to proceed via ring closure to **208** followed by sulfur extrusion (87MI2) (Scheme 56).

G. 1,2-THIAZOLE DERIVATIVES FROM DITHIAZINES

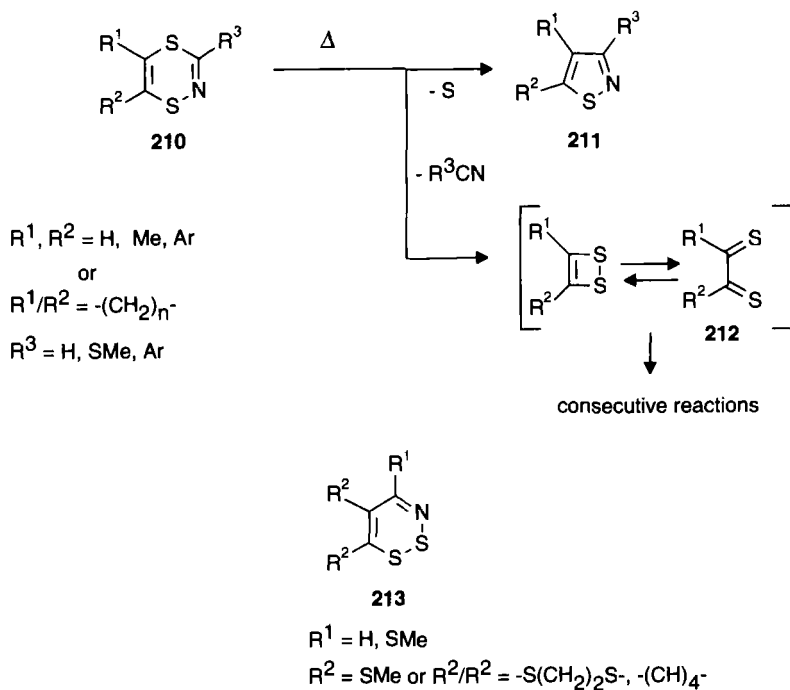
Several isothiazoles **211** are accessible by thermal sulfur extrusion from the corresponding 1,4,2-dithiazines **210**. As a side reaction, elimination of MeSCN ($\text{R}^3 = \text{SMe}$) is observed, affording reaction products via 1,2-dithiones **212**. If the dithiazines **210** are unsubstituted in the 3-position ($\text{R}^3 = \text{H}$) or if photolytic conditions are used ($\text{R}^3 = \text{Ar}$), the analogous elimination of R^3CN is the sole reaction [65ZC386; 76JPR(318)127; 87MI3; 94JCS(P1)2571] (Scheme 57). The formation of isothiazoles from 1,2,3-dithiazines **213** was also observed (Scheme 57) [92T8143; 94JCS(P1)2571].

H. 1,3-THIAZOLE DERIVATIVES FROM DITHIAZINES

In the 1,2,4-dithiazine series, sulfur extrusion was used for the synthesis of several antibiotic β -lactam derivatives **215** (82CC809, 82CC1119;



SCHEME 56



SCHEME 57

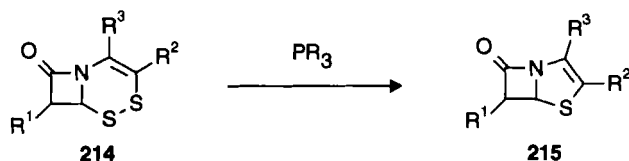
83TL1631) (Scheme 58). In this reaction, retention of configuration was observed (83TL1631), leading to the suggestion of zwitterionic intermediates **216** (82CC809).

In a similar reaction, azetidinothiazolines **218** were prepared from the corresponding dithiazines **217** (79CP1063610) (Scheme 59). Compounds containing the 1,3-thiazolidine ring are also formed in the reaction of bicyclic oligosulfides of 2,5-diketopiperazines with PPh_3 (see Section VI, Scheme 75).

IV. Four-Membered Rings from Five-Membered Rings

A. CYCLOBUTANE DERIVATIVES FROM THIOPHENES

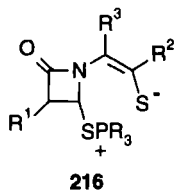
The desulfurization of tetrahydrothiophene by ozone/oxygen (81MI1) or arc-generated singlet carbon gives low yields of cyclobutane **219** and ethene



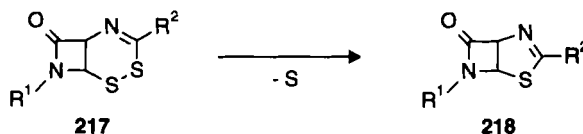
$\text{R}^1 = \text{H, Cl, CH(Me)OR}$

$\text{R}^2 = \text{Me, SAc}$

$\text{R}^3 = \text{CO}_2\text{Alk}$



SCHEME 58

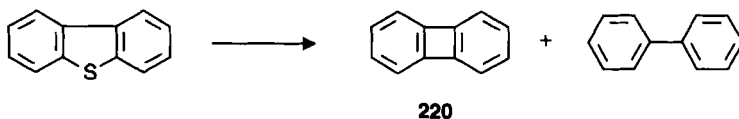
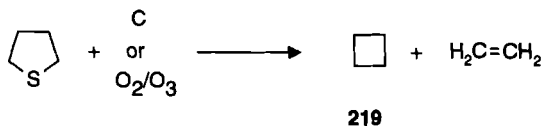


$\text{R}^1 = \text{Alk}$

$\text{R}^2 = \text{CHO, Alk}$

SCHEME 59

as the major product (71JA3807) (Scheme 60). Biphenylene **220** and biphenyl were found as products when dibenzothiophene was reacted with the bis(1,5-cyclooctadiene)nickel(O)/2,2'-bipyridyl complex at lower conversions (79MI1) (Scheme 60).

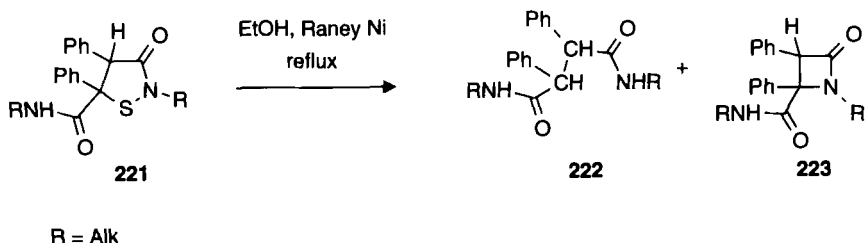


SCHEME 60

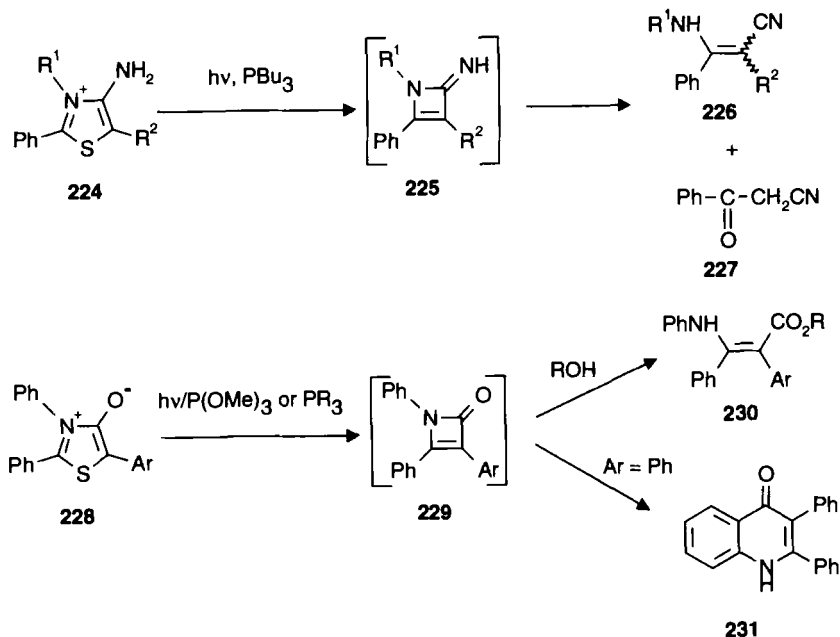
B. AZETINE DERIVATIVES FROM THIAZOLES

Desulfurization of 1,2-thiazolidinones **221** with Raney nickel affords low yields of ring-contracted β -lactams **222** together with ring-opened hydrogenated succinamides **222** (74JOC1210) (Scheme 61). Diradical intermediates are presumed to be involved.

The photochemical desulfurization of 4-amino-1,3-thiazolium salts **224** or mesoionic 2,3,5-triaryl-1,3-thiazolium-4-olates **228** in the presence of trialkylphosphite or trialkylphosphine, affording ring-opened cinnamic acid derivatives **226** [88JCS(P1)189] and **230** (83JHC245) or quinolinones **231** [88JCS(P1)189] is assumed to proceed via intermediate azetine derivatives **225** and **229**, respectively (Scheme 62).

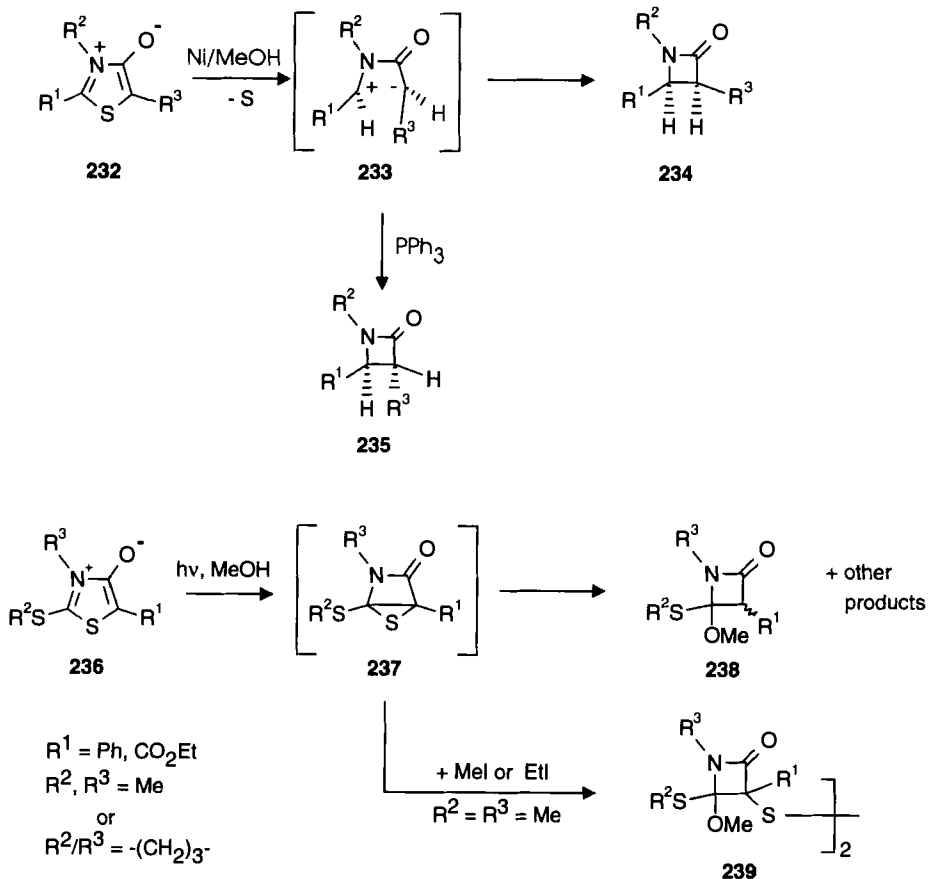


SCHEME 61



SCHEME 62

Azetidinones **234** (78TL2037; 80JOC2165) and **238** [77JCS(P1)1107] can be isolated as ring-contraction products of 1,3-thiazolium-4-olates **232** and **236**, respectively, when highly strained azetidinones are avoided by additions to the endocyclic double bond, i.e., of hydrogen or methanol, respectively (Scheme 63). The high *cis* stereoselectivity of the formation of azetidinones **234** was explained by the fast cyclization of the intermediate zwitterions **233**. In the presence of triphenylphosphine, the latter gave triphenylphosphonium salts cyclizing to the *trans* products **235**. If alkyl iodides are present in the photolytic ring-contraction reaction of zwitterionic 1,3-thiazolium-4-olates **236**, the sulfur atom is maintained, giving bisazetidinone disulfides **239** [77JCS(P1)1107] (Scheme 63).



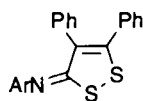
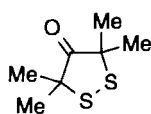
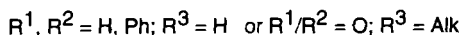
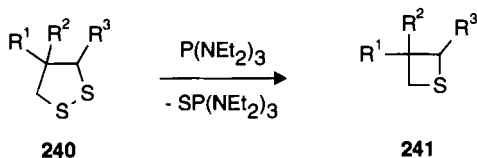
SCHEME 63

C. THIETANE DERIVATIVES FROM DITHIOLANES

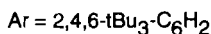
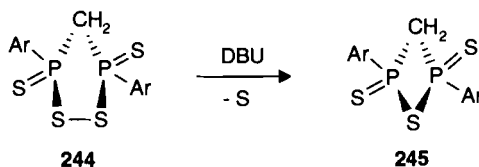
1,2-Dithiolanes **240** can easily be ring-contracted by $P(NEt_2)_3$, affording high yields of thietanes **241** (70JOC3259) (Scheme 64). The analogous reaction of the 1,2-dithiolan-4-one **242**, applying carbenes as desulfurizing agents, gave only low amounts of the corresponding thietanone (85TL5187). Even more strained unsaturated thietimines can be obtained by desulfurization of dithiolimines **243** with tributylphosphine (86CB162).

D. THIADIPHOSPHETANES FROM DITHIADIPHOSPHOLANES

The sterically congested dithiadiphospholane **244** extrudes sulfur in the presence of DBU, affording the thiadiphosphetane **245** with retention of configuration (91CL2213) (Scheme 65).



SCHEME 64



SCHEME 65

V. Three-Membered Rings from Four-Membered Rings

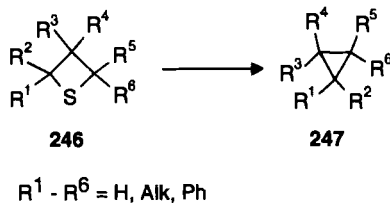
Several thietanes **246**, including spiro and condensed derivatives, have been desulfurized to the corresponding cyclopropanes **247**. In most cases, the reaction is conducted with Raney nickel under reflux. Bulky substituents in the 2- and/or 4-position seem to be favorable (67JOC3676; 72MI3; 76JA2219; 86T4691). The application of singlet carbon atoms also leads to cyclopropanes in low to moderate yields (73JA1547) (Scheme 66). Biradical intermediates may be involved.

VI. Miscellaneous

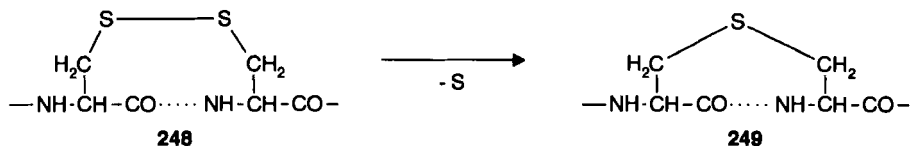
In addition to the reactions just reviewed, there are examples of sulfur extrusions that start with a ring size larger than seven or take place with a ring-size reduction by more than one ring atom.

Cyclic peptides **248** containing cysteine units can lose one sulfur atom by interaction with hexaethyl phosphoric acid triamide, affording ring-contracted structures **249** (83BCJ2044, 83MI2; 86BCJ2505) (Scheme 67).

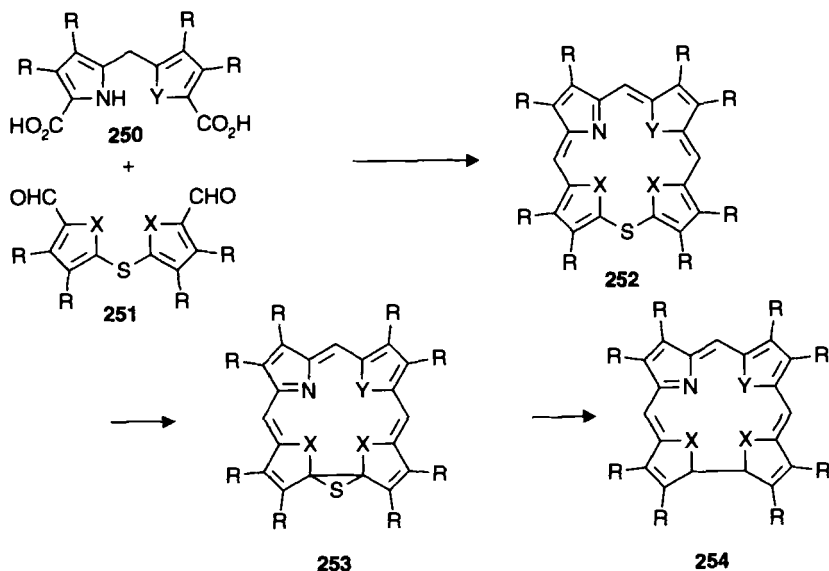
Thiaporphines **252** (X, Y = NH, NR) or their oxa derivatives (X = O, Y = NH, NR) can be synthesized from the two subunits **250** and **251**. As antiaromatic 20π systems, they undergo cheletropic reaction via intermediates **253**, which extrude sulfur either in the course of the preparation or in a consecutive step, yielding the corrins **254** or their oxa analogs [69CC23; 70CC807; 72JCS(P1)1124] (Scheme 68).



SCHEME 66



SCHEME 67

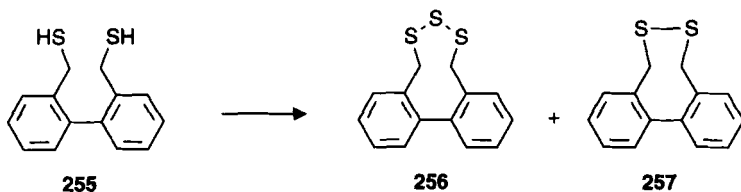


SCHEME 68

Another desulfurization that occurs in the thiocorrin series is one that presumably proceeds via intermediate ring expansion and consecutive ring contraction by the loss of sulfur [67AG865, 67AG(E)866].

Attempts to synthesize trisulfide **256** by sulfuration of dithiol **255** resulted in a mixture of **256** and disulfide **257**. The latter is assumed to be formed by ring contraction of the trisulfane **256** (81JOC2072) (Scheme 69).

The extrusion of both sulfur atoms from dithiacyclophanes (for reviews, see 75MI1; 83MI3) has often been used for the synthesis of various types of ring-contracted cyclophanes (Schemes 70–73). Cyclophanes of type **260** are formed when dithiacyclophanes **258** are reacted with trialkyl phos-



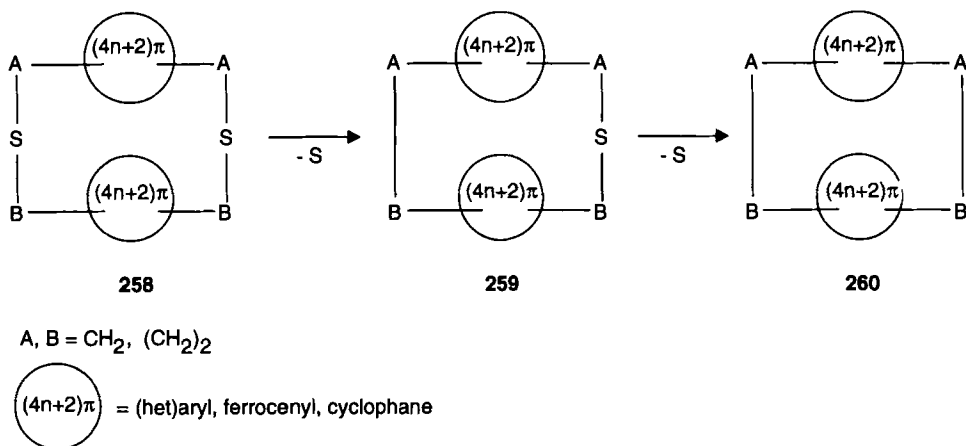
SCHEME 69

phites under photochemical conditions [73AG831, 73AG(E)776, 73C277, 73CC406, 73TL1215; 74TL3053; 75S807; 77CL977; 83JOC1341; 85BCJ2502; 86JFC399, 86LA751; 87BCJ2953; 89CB347, 89JOC5991; 91CB1403; 93JCS(P2)1373] or with $\text{Fe}(\text{CO})_5$ under reflux in toluene [83JOM(243)191] (Scheme 70). In some cases, monothiacyclophanes of type **259** were also detected (73C277, 73CC406; 91CB1403) (Scheme 70).

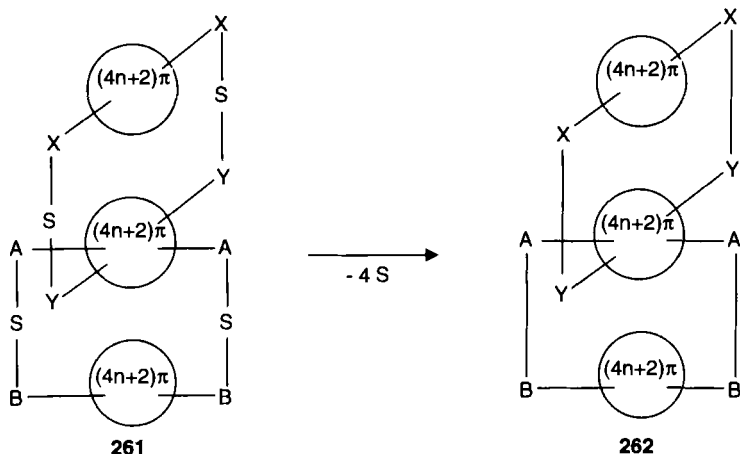
Triple-layered cyclophanes **262** can be synthesized according to Scheme 70 [77CL977; 93JCS(P2)1373] or Scheme 73 [93JCS(P2)703], where one $(4n + 2)\pi$ system in starting material **258** or **265** is already a cyclophane, or by extrusion of four sulfur atoms from a triple-layered tetrathiacyclophane **261** (89BCJ164) (Scheme 71).

Cyclophanes of type **264** are accessible from monothiacyclophanes **263** under pyrolytic conditions (78CB1653) or by photolysis in trialkyl phosphite [86AG1029, 86AG(E)1026; 88AG987, 88AG(E)976; 89CB347] (Scheme 72).

Another route to cyclophanes **268** consists of the thia-Wittig-type rearrangement of dithiacyclophanes **265** in the presence of BuLi or LDA with subsequent *S*-methylation (Scheme 73, Route A) [75TL219; 87BCJ2953; 93CB167, 93JCS(P2)703, 93JCS(P2)1373]. The reversed sequence, i.e., primary *S*-methylation and subsequent Stevens rearrangement (Scheme 73, Route B), also leads to cyclophanes **268**. However, this method does not fully fit into the topic of this review since *S*-methylation products **267** are isolated and hence the SMe group, not the sulfur atom, is extruded (for a review, see 73S85). This method can also be used for the synthesis of triply



SCHEME 70

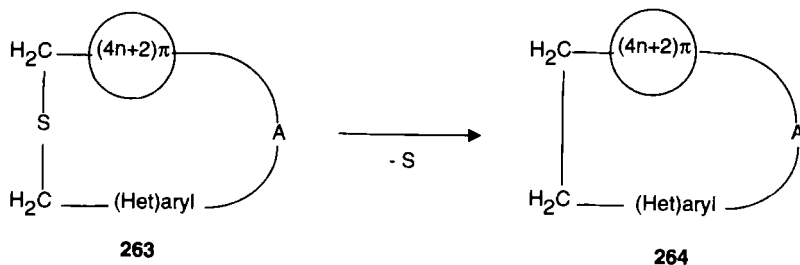


SCHEME 71

bridged cyclophanes. The thiomethyl groups of **268** can be removed in a consecutive step by a reaction with Raney nickel or by a kind of Hofmann elimination affording cyclophane dienes. The latter method can also be applied to the synthesis of triply bridged cyclophane trienes **269**.

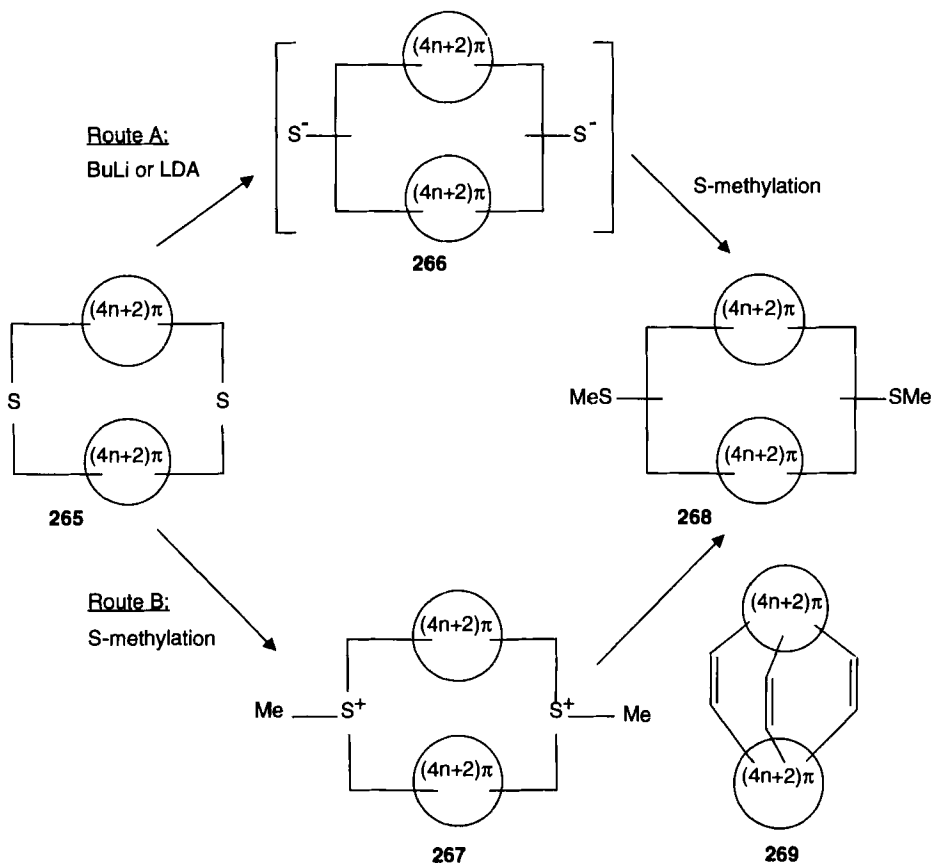
The desulfurization of thiacyclophanes is also possible by oxidation; the resulting sulfones are isolated and ring-contracted by elimination of SO_2 in a subsequent step (for a review, see 73S85).

Although not a genuine sulfur extrusion, the reaction of the tetrathia-cyclophane **270** with $\text{Mo}(\text{CO})_6$, $\text{W}(\text{CO})_6$ [81JOM(212)77], or $\text{Cr}(\text{CO})_6$ [80JOM(202)13; 81JOM(212)77] is worth mentioning. The stepwise loss of both $-\text{S}-(\text{CH}_2)_3-\text{S}-$ units presumably proceeds via a radical mechanism



A = 1,8-naphthylidene, $-\text{CH}=\text{CH}-\text{CH}(\text{Ph})-\text{CH}(\text{Ph})-\text{CH}=\text{CH}-$, $-\text{CH}_2-\text{O}-$

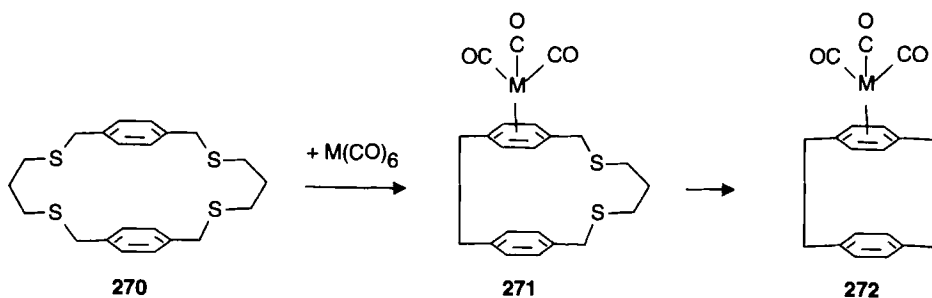
SCHEME 72



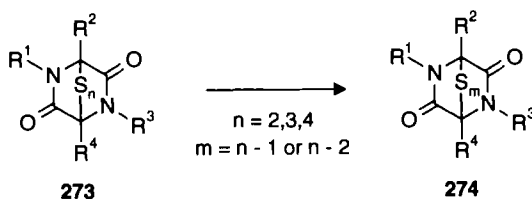
SCHEME 73

and involves the formation of the metal carbonyl/benzene complexes **271** and **272** (Scheme 74).

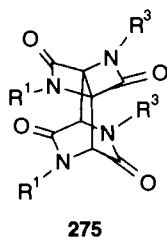
Bicyclic oligosulfides **273** of 2,5-diketopiperazines (71GEP2029305; 74CPB2866; 76T507) or condensed derivatives [69CC1466; 71JCS(C)1189; 76JOC3433; 79JA1159] can eliminate one or two sulfur atoms, affording ring-contracted bicyclic compounds **274** after treatment with PPh_3 . This ring contraction can proceed either with retention or with inversion of configuration, depending on the number of sulfur atoms and to some extent on the kind of the desulfurization reagent employed (70CC811). Sometimes, sulfur-free products such as **275** are obtained from two molecules of **273** (76T507) (Scheme 75).



SCHEME 74



$R^1 - R^4 = H, \text{Alk}, CO_2Et, Ph$



SCHEME 75

When reacted with Raney nickel, dithiolanes **276** lose both sulfur atoms and form the corresponding cyclopropane derivatives **277** (80CC243) (Scheme 76).



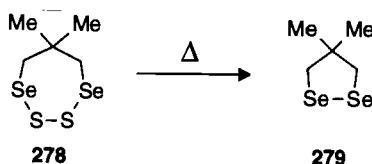
$R = \text{Alk}, \text{Ac}$

SCHEME 76

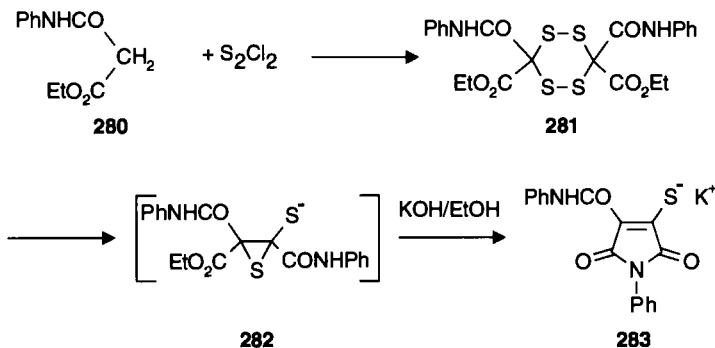
The dithiadiselenacycloheptane **278** forms the corresponding diselenacyclopentane **279** with loss of two sulfur atoms, too [87AG917, 87AG(E)887] (Scheme 77).

Again, the tetrathiane **281**, accessible from the amido ester **280** and S_2Cl_2 , loses more than one ring sulfur atom, forming the maleic imide **283** when reacted with $KOH/EtOH$. The episulfide **282** is assumed to be an intermediate in this reaction [89JCS(P1)1699] (Scheme 78).

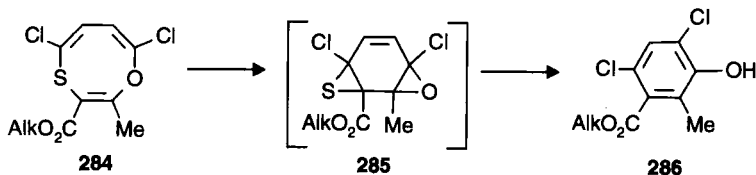
1,4-Oxathiocines **284** reduce their ring size by two atoms on heating at reflux in toluene or chlorobenzene, yielding phenols **286**. Intermediates **285** may extrude the sulfur atom by a cheletropic process accompanied by a 1,2-chlorine migration in the course of the α -chloroepoxide ring opening (88CC138; 91PS161) (Scheme 79). Similar reactions were reported for the analogous 1,4-dithiocines [71JA4627; 74AG381, 74AG(E)345].



SCHEME 77



SCHEME 78



SCHEME 79

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Carbenes and Carbenoids in Synthesis of Heterocycles

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Abbreviations: acac, acetylacetonate; acam, acetamide, BINAP, binaphtholphosphate; BNOX, 4-benzyl-2-oxazolidinone; cap, caprolactamate; DMAD, dimethyl acetylenedicarboxylate; hfacac, hexafluoroacetylacetonate; MACIM, methyl 1-acetylimidazolidin-2-one-4-carboxylate; MEPY, methyl 2-pyrrolidone-5-carboxylate; MEOX, methyl 2-oxazolidinone-4-carboxylate; NPMI, *N*-phenylmaleimide; pfb, perfluorobutyrate; oct, octanoate; TEBA, benzyltriethylammonium chloride; tfa, trifluoroacetamidate.

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I. Introduction

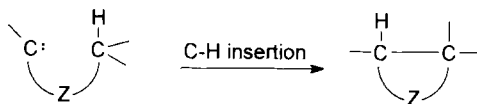
The primary purpose of this review is to summarize the ongoing utility of carbenes in heterocyclic synthesis. Several excellent reviews on the synthetic aspects of carbene chemistry have recently appeared (87MI1; 89HOU2, 89UK1250; 91ACR22, 91CRV263; 92MI4, 92MI5, 92T5385; 93IZV646, 93T5203; 94AG1881, 94CRV1091). However, the reviews devoted to the application of carbenes in heterocyclic chemistry were published fairly long ago (64AHC57; 76KGS1443; 81AHC231; 82KGS723). The present review covers the literature between 1979 and early 1995. Moreover, reference to earlier research articles or to existing reviews has been made where it seemed appropriate.

Of the three classes of divalent carbon species—free carbenes, reactive transition-metal carbene complexes (carbenoids), and stable metal carbenes—we restrict our consideration to the first two. Taking into account the fact that a fine reaction mechanism in planning the synthesis of specific molecules is of secondary importance, we discuss carbene and carbenoid reactions together. We concentrate solely on reactions and reaction sequences that result in a formation of a new heterocycle. Within subsections, the material is organized on the basis of reaction type.

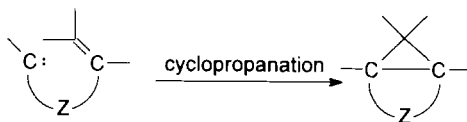
II. General Carbene Routes to Heterocycles

Three principal carbene-based approaches to the construction of heterocycles can be recognized. These include (1) the carbene cyclization reaction, (2) ring contraction or expansion with carbene intermediacy, and (3) cyclization or cycloaddition of unstable primary products of carbene reactions.

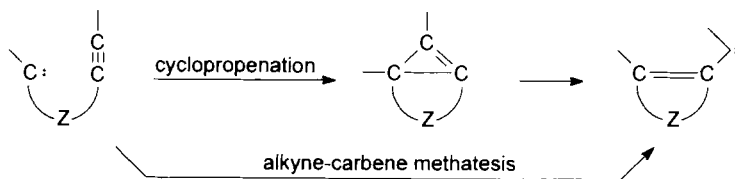
1. The first approach is realizable via a variety of typical carbene reactions. Cyclizations not involving a heteroatom include formation of a new C—C bond as a result of an intramolecular C—H insertion of a carbene (Scheme 1) or its addition onto multiple carbon-carbon bonds [intramolec-



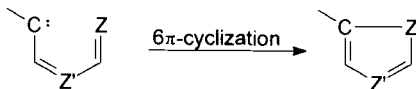
SCHEME 1



SCHEME 2



SCHEME 3

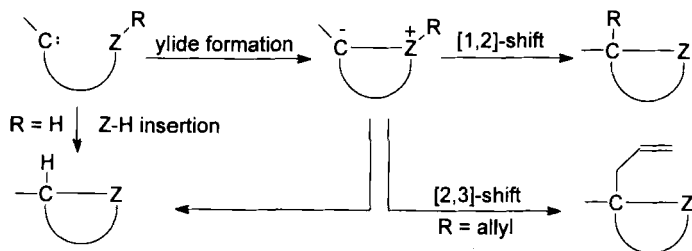


SCHEME 4

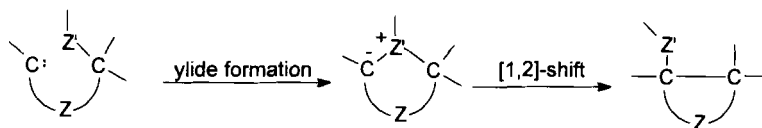
ular cyclopropanation (Scheme 2) and cyclopropenation or alkyne-carbene methatesis (Scheme 3)]. Cyclizations involving a heteroatom leading to formation of a new C—Z bond generally occur via ylides. The sole exception is a 6 π -cyclization of a carbene (Scheme 4).

Intermediate heterocyclic ylides may be stabilized by [1,2]- or [2,3]-rearrangements (Scheme 5). The [1,2]-shift may result in expelling an "ylide" heteroatom from the initially formed ylide (Scheme 6). The 1,3-dipolar cycloaddition of ylides generated by carbene cyclization onto the heteroatom of the C=Z double-bond allows an additional ring to be formed and provides a route to bridged and bridged-fused systems (Scheme 7).

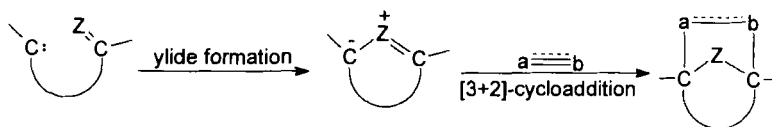
2. The second approach involves ring modification. Ring-contraction carbene reactions include the Wolff-like rearrangement (Scheme 8), transannular formation of an ylide (Scheme 9), or C—H insertion followed by ring fragmentation (Scheme 10). Ring expansion may be effected via both inter- and intramolecular carbene reactions. The former involve ylide formation through addition of a carbene onto the ring heteroatom with subsequent [1,2]- or [2,3]-sigmatropic rearrangement (Scheme 11), as well as 1,1-cycloaddition of a carbene onto the heterocyclic double bond followed by the opening of the three-membered ring (Scheme 12). Intramolecular ring-expansion reactions involve a [1,2]-shift to a carbene center (Scheme 13) and photolytic generation of oxycarbenes from ketones (Scheme 14).



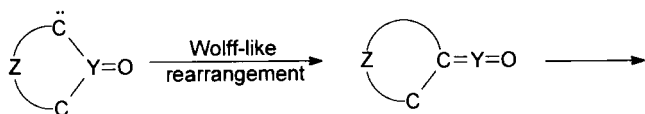
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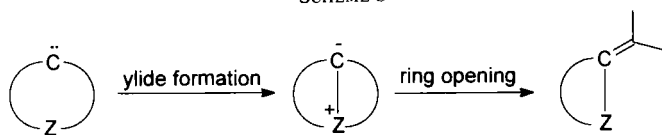
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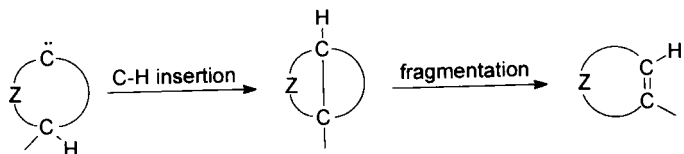
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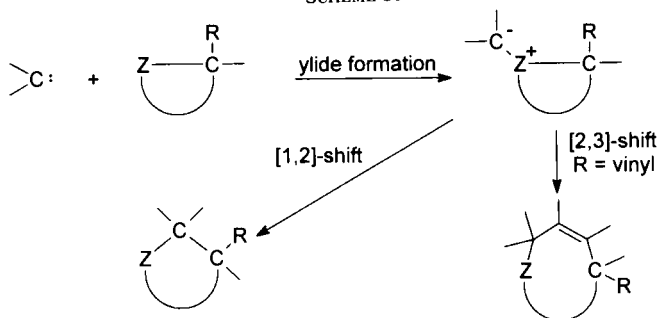
SCHEME 8



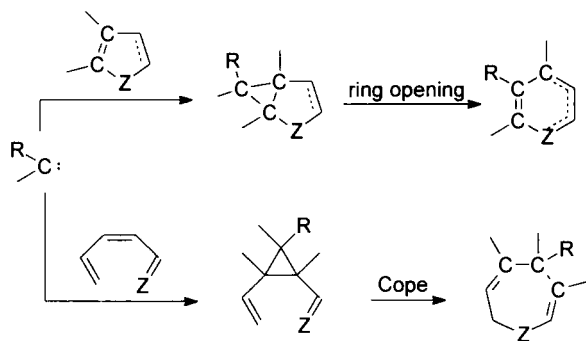
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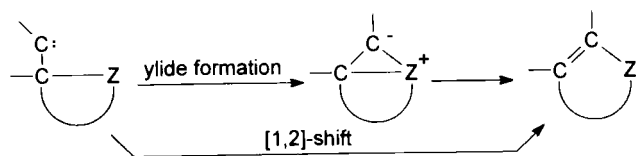
SCHEME 10



SCHEME 11



SCHEME 12



SCHEME 13



SCHEME 14

3. The third carbene-based approach to heterocycles consists in cyclization or cycloaddition of unstable intermediates of carbene reactions. Intramolecular carbene addition to the heteroatom of $C=Z$ bond produces an ylide capable of being stabilized via 1,3- or 1,5-cyclization or via $[3 + 2]$ -cycloaddition (Scheme 15).

Carbenes with a $C=Z$ bond adjacent to the carbenic center may react with multiple bonds, yielding either three- or five-membered heterocycles. The latter may result from the opening of an intermediate carbocycle or from carbene $[3 + 2]$ -cycloaddition (Scheme 16).

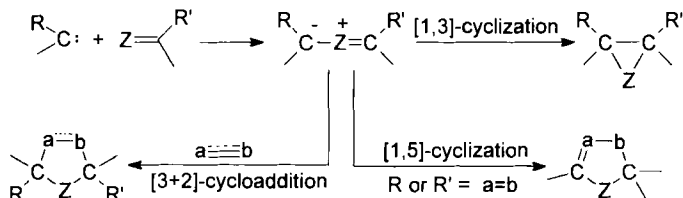
A special case occurs in compounds with a $C=Z$ bond ($Z = P, Si$) arising from a $[1,2]$ -shift to a carbene center (Scheme 17). The formation of heterocycles from these compounds occurs via $[2 + 2]$ - and $[4 + 2]$ -cycloaddition reactions.

The utility of the above routes for the synthesis of particular heterocyclic systems are considered in the relevant sections of the review.

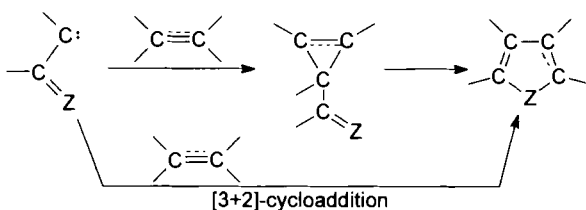
III. Synthesis of Rings with One Nitrogen Atom

A. THREE-MEMBERED RINGS

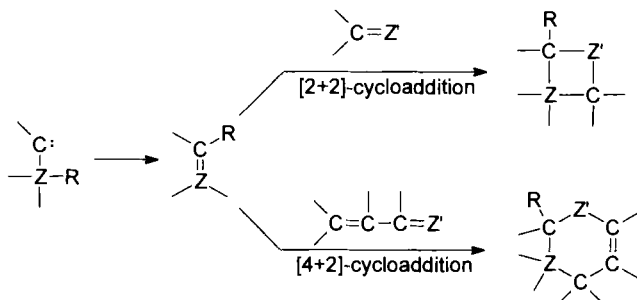
The addition of carbenes to a carbon–nitrogen double bond has proved to be useful for the synthesis of aziridines. After Fields and Sandri [59CI(L)1216] discovered the formation of 1,3-diphenyl-2,2-dichloroaziridine by the reaction of *N*-benzylideneaniline with dichlorocarbene, a wide range of aziridines (**1**) have been obtained by the reaction of $:CBr_2$, $:CBrCl$, $:CBrF$, $:CCl_2$, $:CClF$, $:CF(CO_2Et)$, and $:CH(CO_2Et)$ with imines [for a



SCHEME 15



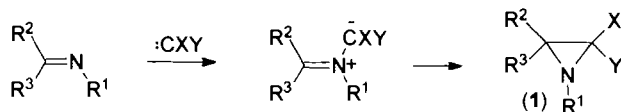
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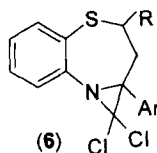
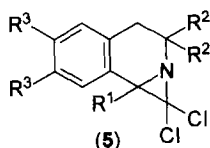
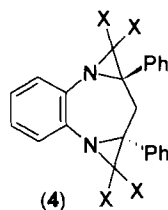
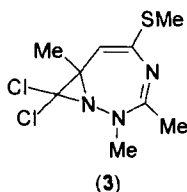
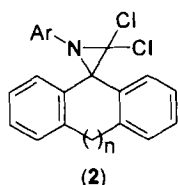


SCHEME 17

review of earlier work, see (76KGS1443; 83MI1)]. It has been shown that the dichlorocarbene reaction with *N*-benzylideneaniline proceeds through transient formation of an azomethine ylide (93MI1).

Although traditional methods of dichlorocarbene generation by the reaction between CHCl_3 and *t*-BuOK continue to be used [e.g., **1** ($\text{R}^1 = \text{R}^2 = \text{Ar}$, $\text{R}^3 = \text{Me}$) was obtained in 41–88% yield (85MI1)], the phase-transfer catalysis method is most convenient for the synthesis of *gem*-dichloroaziridines (74RC2129, 74ZC469; 75URP482448). This method of dichlorocarbene generation was used in the synthesis of 1-(α -campholenyl)-2,2-dichloro-3-arylaziridines (60–95%) (79BAP447), *N*-*tert*-butyl-2,2-dichloro-3-arylaziridines (50%) [91MI1; 96ZOR(ip)], spiroaziridines **2** ($n = 0, 2$) (65–88%) (79H637; 86KGS895), and *N*-fluoroalkyl tetrachloroaziridines (92TL2339). *Gem*-Dibromo- (84KGS912) and *gem*-chlorofluoroaziridines (94UP1) may also be synthesized under phase-transfer conditions. The addition of dihalogenocarbenes to the $\text{C}=\text{N}$ bond of heterocycles affords the corresponding azirino-fused rings such as **3** (40%)

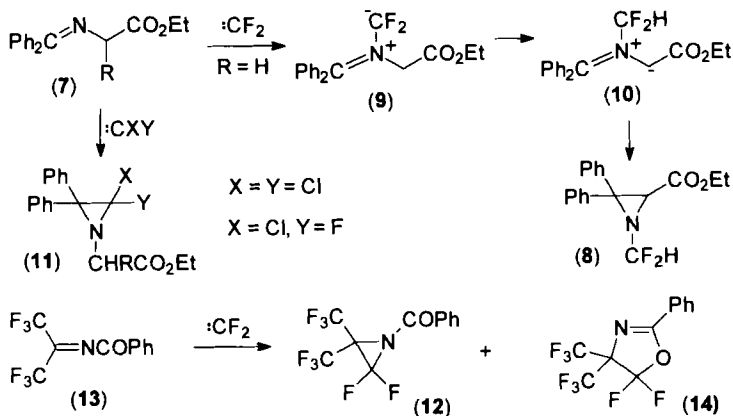




(85RTC129), **4** ($R = \text{H, Cl; X} = \text{Cl, Br}$) (22–55%) (87JHC797), **5** ($R^1 = \text{H, Me; R}^2 = \text{Me, Et; R}^3 = \text{H, OMe}$) (80–100%) [90KGS1086; 92MI2; 96ZOR(ip)], and **6** ($R = \text{Me, Ar}$) (92MI1).

Reaction of glycinate **7** ($R = \text{H}$) and CHClF_2 under ion-pair extraction conditions provides aziridine **8**. The formation of **8** presumably involves the addition of $:\text{CF}_2$ onto the imine nitrogen, generating ylide **9**; this is followed by prototropic shift to form ylide **10**, which then undergoes ring closure (87CC469). Surprisingly, with $:\text{CCl}_2$ and $:\text{CFCl}$ imines **7** ($R = \text{H, Me}$) give “normal” products **11** in good yields (94UP1).

Aziridine **12** was obtained as a by-product in the reaction of imine **13** and CF_2 derived from perfluoropropylene oxide to give **14** (79IZV1826). It is unclear whether the reaction mechanism includes the addition of $:\text{CF}_2$, the most electrophilic dihalogenocarbene, onto the $\text{C}=\text{N}$ bond of imine **13**.

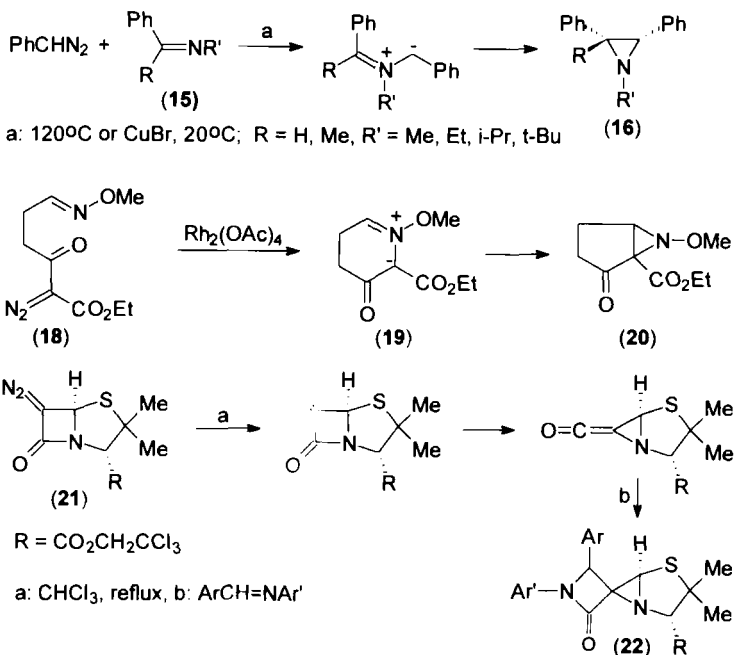


Decomposition of phenyldiazomethane in the presence of imines **15** affords a *trans*-azomethine ylide, which undergoes conrotatory cyclization to give *cis*-aziridines **16** in low yields. The competitive process is [3 + 2]-cycloaddition of ylide to **15** (R = Me, Et; CuBr catalyst) leading to the corresponding imidazolidine (84T2569). The Rh(II)-catalyzed decomposition of diazo compounds **18** results in cyclization of the initially formed carbenoid onto the nitrogen atom to produce intermediate ylide **19**, which gives aziridine **20** in just 9% yield. The main route of stabilization of ylides related to **19** is [3 + 2]-cycloaddition to dipolarophiles (Section IX,A) (94JOC5347).

A ring-contraction reaction is rarely used to produce an aziridine. A Wolff ring contraction of a carbene generated from 6-diazopenicillanate **21** forms the intermediate ketene, which is then trapped by imines to give spiroaziridines **22** (86CC584).

B. FOUR-MEMBERED RINGS

Intramolecular insertion of carbenes into N—H and C—H bond are most frequently used for generating azetidine derivatives. But while carbene

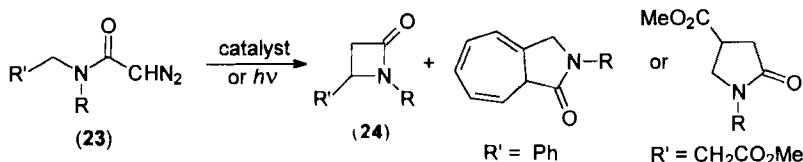


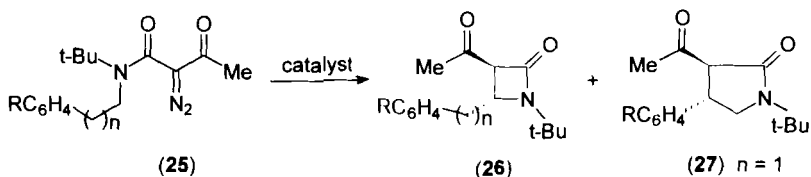
N—H insertion generally proceeds unidirectionally, C—H insertion leading to a four-membered ring is not infrequently accompanied by C—H insertion, yielding a five-membered ring, and also by aromatic cycloaddition, ylide formation, etc. Few other carbene reactions are employed in the synthesis of azetidines, and their mechanisms are not always clear.

1. Intramolecular Insertion Reactions

Intramolecular insertion of carbenoids, arising from catalytic decomposition of α -diazoacetamides, into the C—H bonds of substituents at the amide nitrogen atom is commonly used to produce a β -lactam ring. However, the C—H insertion leading to 3-unsubstituted azetidin-2-one seldom dominates in the decomposition of α -unsubstituted α -diazoacetamides **23**, in which the reaction selectivity depends dramatically on the catalyst. Thus, compound **23** ($R = t\text{-Bu}$, $R' = p\text{-NO}_2\text{C}_6\text{H}_4\text{CH}_2$) gives less than 15% of the corresponding β -lactam **24**. With compound **23** ($R = t\text{-Bu}$, $R' = \text{Ph}$), however, using $\text{Rh}_2(5S\text{-MEPY})_4$ as the catalyst ensures that C—H insertion product β -lactam **24** ($R = t\text{-Bu}$, $R' = \text{Ph}$) predominates over the aromatic cycloaddition product (93JA8669). At the same time, a $p\text{-NO}_2$ substituent can substantially limit cycloaddition to the aromatic ring, and compound **23** ($R = t\text{-Bu}$, $R' = p\text{-NO}_2\text{C}_6\text{H}_4$) yields exclusively the corresponding β -lactam **24** (88JOC3384). The Rh(II)-catalyzed decomposition of compounds **23** ($R = t\text{-Bu}$, $R' = \text{Pr}$, $t\text{-Bu}$, MeO_2CCH_2) affords predominantly γ -lactams, but if $\text{Rh}_2(4S\text{-BNOX})_4$ is the catalyst, β -lactam **24** ($R = t\text{-Bu}$, $R' = \text{MeO}_2\text{CCH}_2$) is the major product (92TL7819). Treatment of N,N -diisopropyl α -diazoacetamide with Rh(II) acetate, perfluorobutyrate, or 2-phenoxybenzoate yields the corresponding β - and γ -lactams in 4.2:1, 2.4:1, and 6.2:1 ratios, respectively (88JOC3384). Photolysis of N,N -diethyl- or N,N -dimethyl- α -diazoacetamides produces the corresponding β -lactams along with acyclic products (79JOC3072; 81JOC1090).

Rhodium(II) carboxylate-catalyzed decomposition of diazoacetamides (versus diazoacetamides) is a more efficient method for generating a β -lactam ring by carbenoid C—H insertion. Treatment of ring-substituted N -benzyl- N -tert-butyl diazoacetamides **25** ($n = 0$) with $\text{Rh}_2(\text{AcO})_4$ results in the exclusive production of β -lactams **26** ($n = 0$) in 90–98% yield

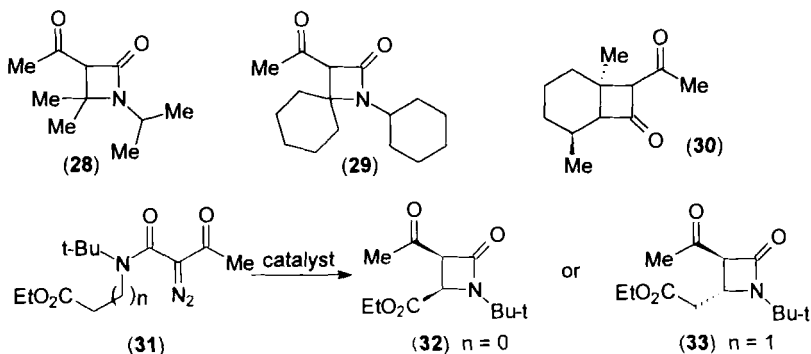




(88JOC3384). The introduction of an additional methylene unit into the linker leads to formation from **25** ($n = 1$; $\text{R} = \text{H}$) of β -lactam **26** ($n = 1$; $\text{R} = \text{H}$) and γ -lactam **27** ($\text{R} = \text{H}$); the former lactam predominating only when $\text{Rh}_2(\text{pfb})_4$ is used as the catalyst (93JA8669).

The presence of a bulky group or a rigid ring at the nitrogen atom is essential to the success of β -lactam formation. The $\text{Rh}_2(\text{OAc})_4$ -catalyzed decomposition of the diazoacetamides derived from diisopropylamine, dicyclohexylamine, and *trans*-2,6-dimethylpiperidine affords azetidinones **28–30** in 85, 100, and 90% yields, respectively (88JOC3384). Diazoacetamides **31** ($n = 0, 1$) react to give *cis*- and *trans*-azetidinones **32** and **33**. The observed stereoselectivity is explained by a conformational preference that juxtaposes the carbenoid center and the less sterically hindered amide substituent (89TL5397). With a chiral catalyst, optically active **33** was obtained in 93% yield and 26% e.e. (92TL5983).

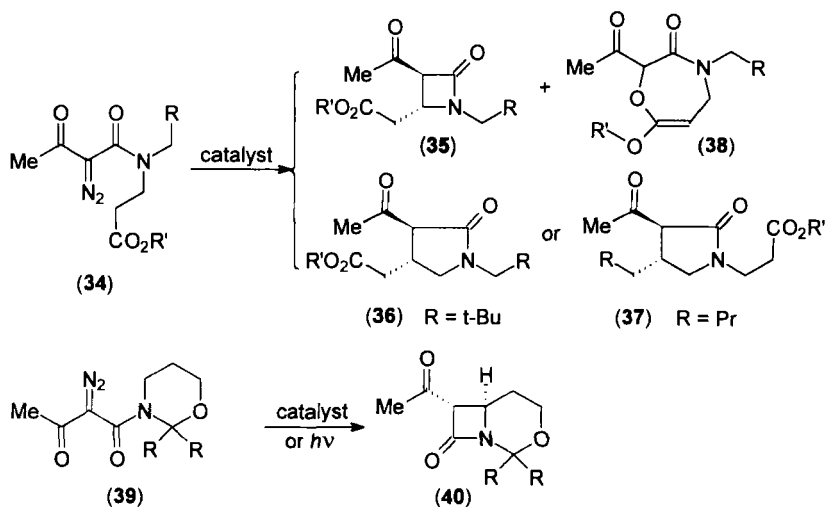
The $\text{Rh}(\text{II})$ -catalyzed decomposition of diazoacetamides **34** ($\text{R} = t\text{-Bu}$, Pr ; $\text{R}' = \text{Et}$, $t\text{-Bu}$) leads to both β -lactams **35** and γ -lactams **36** or **37**; in addition, the azaoxepinone **38** is formed. The product distribution is strongly influenced by the substituents R and R' and by the nature of the catalyst. Thus, the decomposition of diazo compound **34** ($\text{R} = \text{R}' = t\text{-Bu}$) with $\text{Rh}_2(\text{pfb})_4$ in refluxing benzene results in the exclusive production of β -lactam **35** ($\text{R} = \text{R}' = t\text{-Bu}$) (91JOC820), whereas **34** ($\text{R} = \text{Pr}$, $\text{R}' = \text{Et}$) yields no β -lactam under the same conditions (89TL5397; 91JOC820).

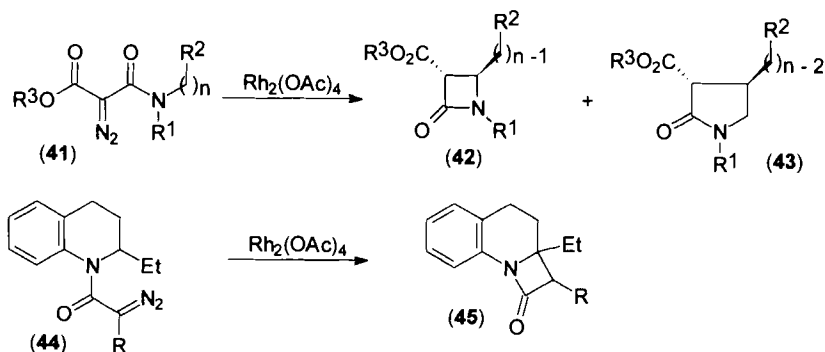


Compound **34** ($R = t\text{-Bu}$, $R' = \text{Et}$) gives mostly **35** with $\text{Rh}_2(\text{acam})_4$ as a catalyst (89TL5397).

Photolytic and catalytic decomposition of diazoacetamides, where an amide nitrogen is incorporated into the six-membered ring, results in 1-azabicyclo[4.2.0]octane derivatives via azetidinone ring formation. Tetrahydrooxazines **39** [$R = \text{Me}$; $R + R = (\text{CH}_2)_5$] on irradiation cyclize to give exclusively the *trans*-substituted β -lactam product **40** [$R = \text{Me}$, 55%; $R + R = (\text{CH}_2)_5$, 73%]. Cyclization of **39** has also been successful using $\text{Rh}_2(\text{OAc})_4$ (79CC846). Catalytic transformations of optically active derivatives of **39** were employed in the stereocontrolled synthesis of carbapenem derivatives (84TL2913; 86TL247).

α -Diazoacetamides containing an α -arylsulfonyl or α -alkoxycarbonyl group are also used in β -lactam synthesis. Photolysis of α -diazo- α -phenylsulfonylacetopiperidide give a 60% yield of *trans*-7-phenylsulfonyl-1-azabicyclo[4.2.0]octan-8-one as a result of carbene insertion into a C—H bond of the piperidine ring (86AJC687). Rhodium carbenoid from *N*-alkyl- α -alkoxycarbonyl- α -diazoacetanilide **41** inserts into the C—H bond of the *N*-alkyl substituent, yielding azetidin-2-one **42** and/or pyrrolidin-2-one **43**, depending on the *N*-alkyl chain length. The $\text{Rh}_2(\text{OAc})_4$ -catalyzed reaction of diazoanilides **41** ($n = 1$; $R^1 = \text{Ph}$, $p\text{-MeOC}_6\text{H}_4$; $R^2 = \text{H}$, Me , Ph ; $R^3 = \text{Me}$, Et) gives β -lactams **42** as the only detectable products (92JOC4404; 94JOC2447). However, diazoacetanilides **41** with longer-chain alkyl substituents ($n = 2, 3$; $R = \text{Et}$, Ph , $\text{H}_2\text{C}=\text{CH}$) yield 0–17% of the corresponding β -lactams. The major products here are γ -lactams **43** (54–81%) (92JOC4404). The bicyclic α -methoxycarbonyl- α -diazoacetamide **44** ($R =$



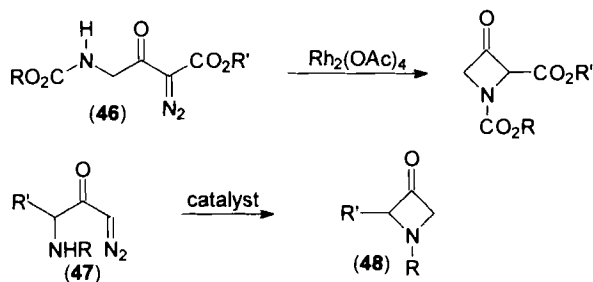


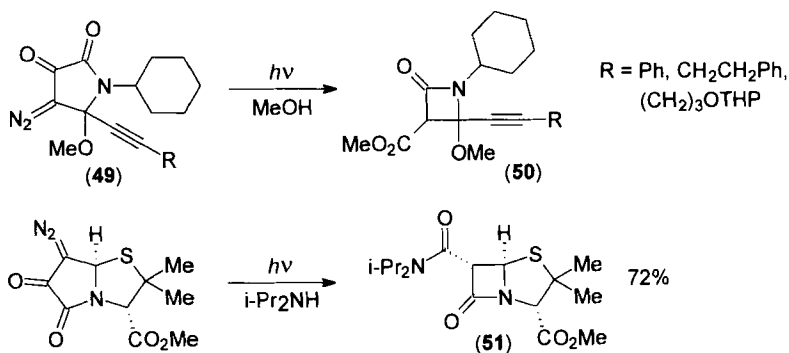
CO_2Me) affords **45** ($\text{R} = \text{CO}_2\text{Me}$) in 85% yield, while acetyl-substituted **44** ($\text{R} = \text{Ac}$) gives no more than 2% of the corresponding azetidinone (92JOC4404).

Metal-catalyzed decomposition of diazo compounds with a monosubstituted amide group at the β -position allows production of azetidine derivatives resulting from the insertion of a carbenoid into the $\text{N}-\text{H}$ bond. Thus, the $\text{Rh}_2(\text{OAc})_4$ -catalyzed reaction of α -diazo β -keto esters **46** ($\text{R} = \text{PhCH}_2$, $\text{R}' = \text{Me}$; $\text{R} = \text{R}' = t\text{-Bu}$) affords the corresponding 2-alkoxycarbonyl-3-oxoazetidines in good yields (85JOC5223; 92T7165). In the presence of $\text{Cu}(\text{hfacac})_2$, α -diazo ketones **47** ($\text{R} = \text{Ts}$; $\text{R}' = \text{H}$, Me , Ph) undergo smooth decomposition to the corresponding 3-azetidinones **48** almost quantitatively (85G33). The $\text{Rh}(\text{II})$ -mediated diazo ketone (R)-**47** ($\text{R} = \text{Boc}$, $\text{R}' = t\text{-BuPh}_2\text{Si}$) insertion reaction leading to (L)-3-azetidinone **48** was used in the total synthesis of (+)-polyoximic acid (93TL4157).

2. Miscellaneous Reactions

Another synthetic route to β -lactams involves the photolytic ring contraction of 4-diazopyrrolidine-2,3-diones. Diazo compounds **49** undergo Wolff

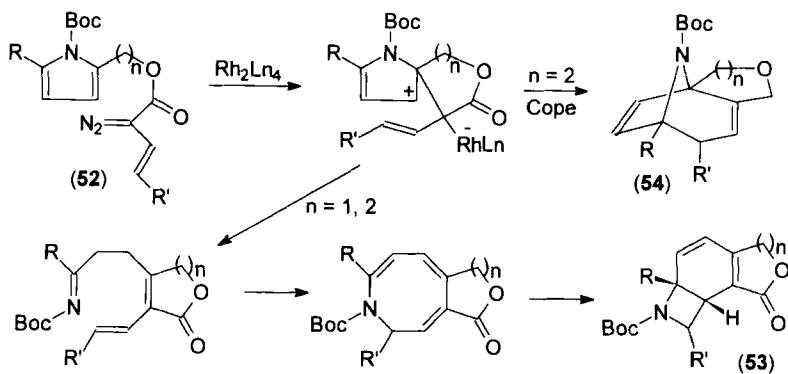




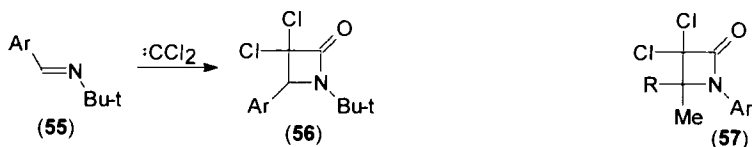
rearrangement (acyl migration) to form azetidinones **50**, isolated as a mixture of (*Z*)- and (*E*)-isomers in 63–74% yield. This transformation was applied to the synthesis of bicyclic lactam **51** (83JOC3365).

Intramolecular capture by pyrroles of vinylcarbenoids generated by Rh₂(oct)₄-catalyzed decomposition of α -vinyl- α -diazo esters **52** ($n = 1$; R = H, Me; R' = H, Ph) results in the formation of the corresponding 7-azabicyclo[4.2.0]octadienes **53** in 34–79% yield. The higher homolog **52** ($n = 2$; R = H, R' = Ph) with rhodium(II) *N*-(*p*-(*tert*-butyl)phenylsulfonyl)-prolinate as catalyst affords 51% azetidine **53** ($n = 2$; R = H, R' = Ph) and 24% tropane **54** ($n = 2$; R = H, R' = Ph). A reasonable mechanism to explain this transformation is shown in Scheme 18 (94TL5209).

Surprisingly, with dichlorocarbene generated by another method (thermocatalytic decomposition of sodium trichloroacetate instead of alkaline hydrolysis of chloroform under phase-transfer catalysis conditions) *N*-(*p*-R-benzylidene)-*tert*-butylamines **55** (R = H, Cl) give 3,3-dichloroazetidi-



SCHEME 18



ones **56** ($\text{R} = \text{H}, \text{Cl}$) in $\sim 50\%$ yield rather than *gem*-dichloroaziridines [91MI1; 95ZOR(ip)]. Lower yields are obtained when azetidinones **57** ($\text{R} = \text{Et}, \text{c-C}_3\text{H}_5$) are formed from butan-2-one and 1-cyclopropylethanone anils (92ZOR482).

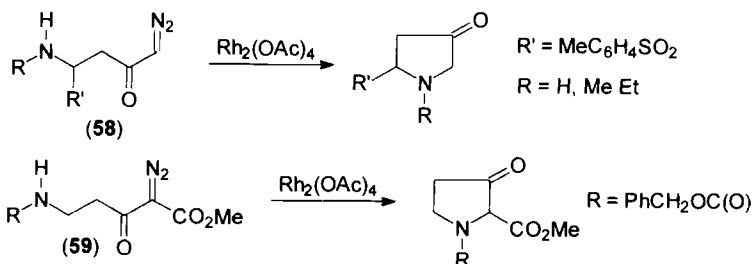
C. FIVE-MEMBERED RINGS

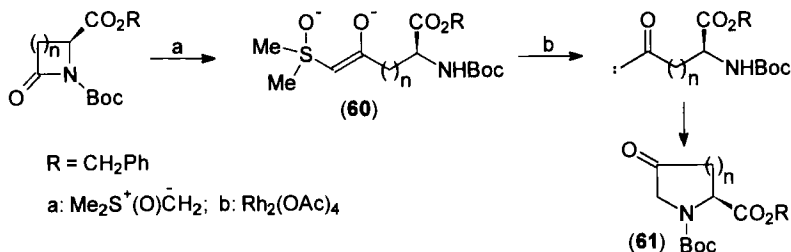
Carbene reactions provide a versatile approach to the synthesis of five-membered nitrogen-containing rings. Of particular importance here are intramolecular insertion of a carbene into C—H and N—H bonds, addition onto multiple carbon-carbon bonds, intermediate formation of ylides as a result of carbene addition onto the heteroatom followed by rearrangement, cycloaddition, and cyclization.

1. Intramolecular N—H Insertion Reactions

When the carbene and amine centers are separated by a three-carbon chain, carbene insertion into the N—H bond results in the formation of pyrrolidine derivatives. Both α -diazocarbonyl compounds **58** and α -diazo β -keto ester **59** give, under the action of $\text{Rh}_2(\text{OAc})_4$, products of carbenoid insertion into the amide N—H bonds in near quantitative yields.

Not only diazo compounds, but also β -ketosulfoxonium ylides can be converted to carbenoids capable of undergoing intramolecular N—H insertion to form pyrrolidine derivatives. Thus, ylide **60** ($n = 1$) was treated with a rhodium(II) catalyst in boiling benzene to give proline derivative

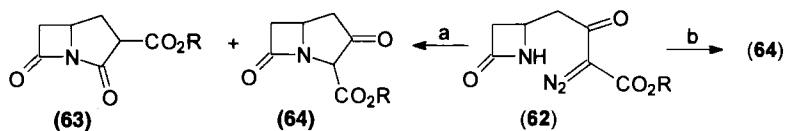




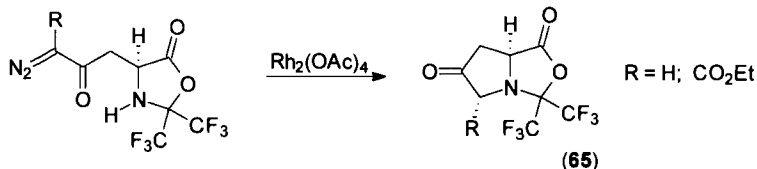
61 ($n = 1$), the highest yield (77%) being attainable with rhodium(II) trifluoroacetate (93CC1434).

The intramolecular insertion into the N—H bond of β -lactams was used successfully in the synthesis of bicyclic ring systems. Photochemical, in contrast to Rh(II)-catalyzed, decomposition of diazo ester **62** was found to occur far less selectively. In the photolytic reaction, the imide **63** is the major product. It presumably arises by a photolytic Wolff rearrangement to a ketene intermediate, which is trapped intramolecularly. With $\text{Rh}_2(\text{AcO})_4$ catalyst the Wolff rearrangement is suppressed and **62** undergoes ring closure to **64** nearly quantitatively (80TL31).

A similar route to the 1-azabicyclo[3.2.0]heptane system was applied in the synthesis of (\pm)-thienamycin (80TL2783; 81JA6765); (+)-thienamycin (80JA6161), 6-epithienamycin (84CC9); 6 β -amidocyclonocardins (81TL5027); 6 α -(1-hydroxyethyl)cyclonocardins (82TL1519); antibiotic (+)-PS-5 [81JCS(P1)2228; 82TL3105; 86JA6054, 86TL3119; 88JOC692; 91JOC5984]; antibiotic PS-6 [81JCS(P1)2228], (+)-PS-6 (91JOC5984); (\pm)-asprenomicin A, B, and C (84TL2237; 85JOC4245); (–)-asprenomicin C (83JA7186); carpetimycins (85TL223); 6-epicarpetimycins (84TL5075); and other carbapenem derivatives [81JCS(P1)1884, 81TL3557; 83CJC1996,



$\text{R} = \text{CH}_2\text{Ph}$; **a**: $h\nu$; **b**: $\text{Rh}_2(\text{OAc})_4$



83TL347; 84CC948, 84TL595; 85TL587; 86JCS(P1)221; 87TL781; 88JOC4154].

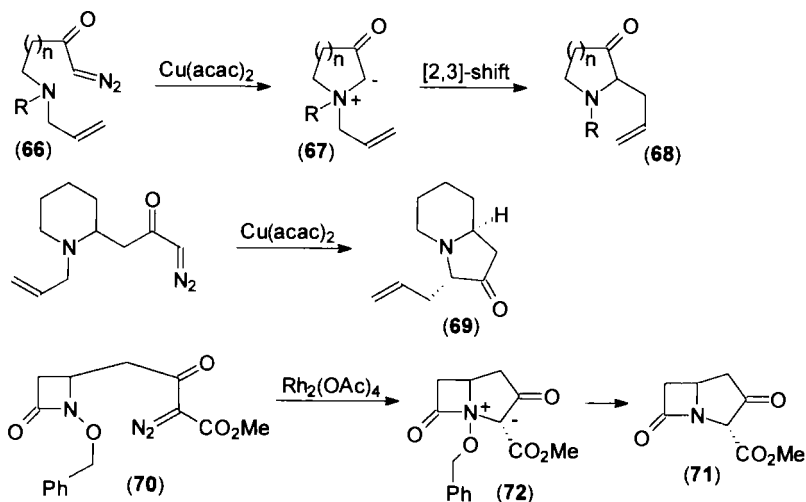
The intramolecular insertion into the N—H bond of γ -lactams can be appropriate for constructing 1-azabicyclo[3.3.0]octane ring systems such as **65** [93AG(E)285].

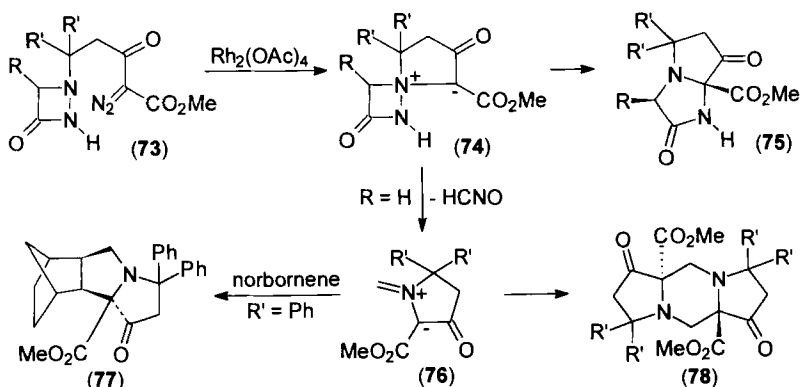
2. Ylide Formation and Subsequent Reactions

Tandem intramolecular formation and rearrangement of ylides from carbenes or carbenoids is a useful method for the preparation of five-membered nitrogen-containing heterocycles. The $\text{Cu}(\text{acac})_2$ -catalyzed intramolecular cyclization of carbenoids derived from diazo compounds **66** ($n = 1$; $\text{R} = \text{Me}$, $\text{c-C}_3\text{H}_5$) affords the ammonium ylides **67**, which then undergo a [2,3]-sigmatropic shift to the corresponding pyrrolidinones **68** in good yields. This sequence was applied to produce indolizidine **69** (94CC2701).

N-Benzyloxy- β -lactam **70** in the presence of $\text{Rh}_2(\text{OAc})_4$ was found to undergo ring closure to provide the carbapenam **71**. The initially generated carbenoid may first interact with a nitrogen electron lone pair to give ylide **72**. Proton abstraction from the benzylic position by this ylide, followed by N—O bond heterolysis, yields the cyclized product and benzaldehyde (90TL1807; 91JOC2688).

An attempt to apply the “normal” carbenoid insertion to aza- β -lactams **73** was unsuccessful. Instead, capture of the carbenoid species by a more





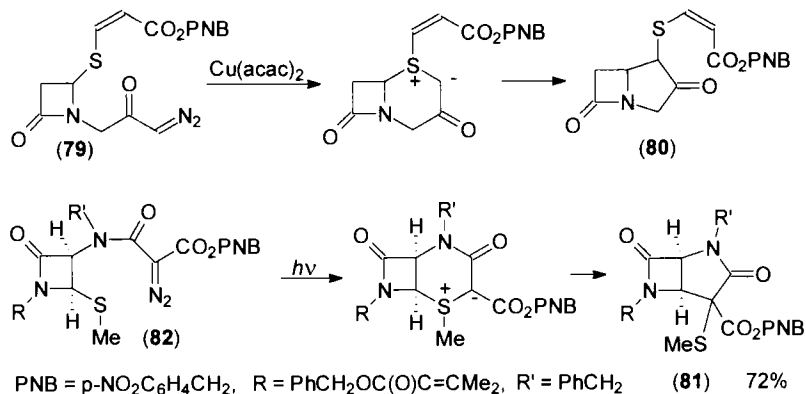
nucleophilic nitrogen occurs to give ammonium ylides **74**, which then react by two competing pathways. Sigmatropic rearrangement of ylides **72** provides yields from 37% (R = H, R' = Ph) to 62% (R = Me, R' = Ph) of 1,4-diazabicyclo[3.3.0]octane **75** (84JOC113).

A tandem process involving carbenoid-mediated intermediate ylide **74** formation followed by fragmentation results in a new ylide **76**. Cycloaddition of the latter to norbornene affords **77** (84JOC113), while dimerization of **76** gives **78**.

An intramolecular carbenoid displacement reaction provided a further process involving a heteroatom, which proved to be useful for constructing pyrrolidine derivatives. Here, S and Se were the heteroatoms participating in ylide formation. Under the action of copper on β -lactam **79**, the intermediate sulfonium ylide rearranges to carbopenam **80** (81H1305). A similar approach was attempted in order to annelate the pyrrolidine ring by stereoselectively introducing a carbon atom at the C₄-position of a β -lactam. Here, Rh(II) catalyst proved to be ineffective, and product **81** was obtained by photochemical decomposition of diazo compound **82** (83H2355).

Intramolecular carbenoid displacement of the diazo sulfide or diazo selenide derivatives **83** is a key step in pyrrolidine ring formation during the synthesis of (\pm)-trachelanthamidine, (\pm)-isoretronecanol, and (\pm)-supinidine [86CC651; 88JCS(P1)833]. Thiocarbonyl ylides generated through carbenoid addition onto a sulfur atom have shown potential as useful intermediates for the synthesis of a variety of alkaloids, e.g., (\pm)-supinidine **84** (94TL3747).

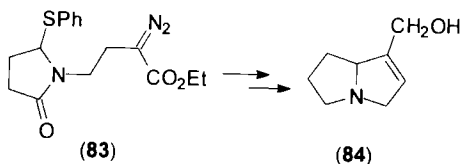
Electrophilic carbenes and carbenoids can readily react with the nitrogen atom of a carbon–nitrogen multiple bond to effect immonium (cycloimmonium) or nitrile ylide formation. 1,3-Dipolar cycloaddition of these ylides

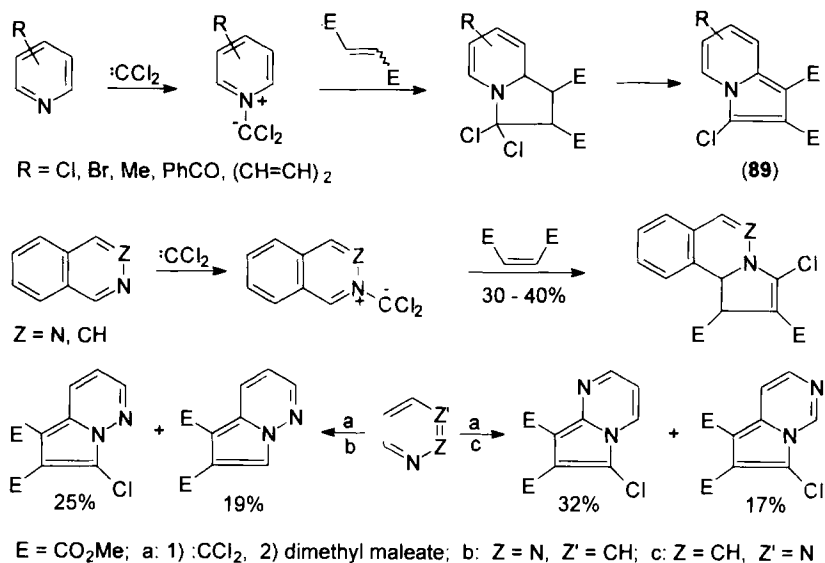


offers a versatile route to a variety of five-membered nitrogen-containing rings.

Unlike aromatic azomethines, *N*-(benzylidene)alkylamines **85** with primary alkyl substituents react with dichlorocarbene to give ylides whose main transformation pathway is not 1,3-cyclization into azirides (cf. Section III,A), but rather stereoselective addition to activated olefins yielding 2-chloropyrrolines **86**. These compounds are readily hydrolyzed during isolation to give the corresponding γ -lactams **87** [91MI1; 95ZOR(ip)]. Dichloromethylides originating from unsubstituted or 3-methyl-substituted 3,4-dihydroisoquinoline and dichlorocarbene add stereoselectively to dimethyl maleate to give **88** [92MI2, 95ZOR(ip)].

1,3-Dipolar cycloaddition of ketene imine (alkylideneazomethine) ylides is a dominant process in the reaction of dichlorocarbene with ketene imines in the presence of activated acetylenes and olefins (Scheme 19). 2,2-Dichloropyrrolidine and pyrrolidine derivatives, which are formed as intermediates in the cycloaddition of ketene imine ylides to substituted acetylenes and ethylenes, respectively, undergo either hydrolysis to give the corresponding lactams or dehydrochlorination to give 2-chloropyrrole derivatives. The pyridine derivatives, which were isolated along with five-membered rings, presumably result from the interaction of ketene imine ylide with trichloromethyl anion followed by addition of the anion to the



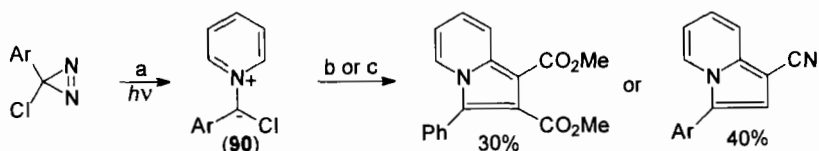


SCHEME 20

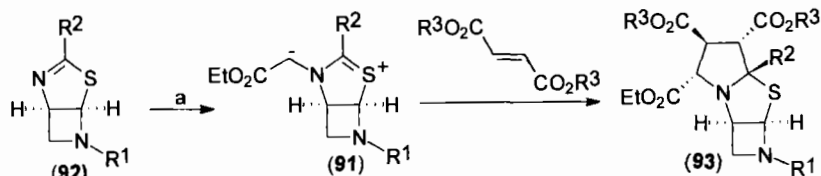
tions, undergo 1,3-dipolar cycloaddition to dimethyl butenedioates to give 3-chloroindolizine derivatives **89** in 45–90% yield. The reaction of 3-substituted pyridines with dichlorocarbene and dimethyl maleate mainly gives 8-substituted indolizines. The cycloaddition of 4-picolinium dichloromethylide to asymmetric dipolarophiles proceeds regioselectively (87KGS856; 90KGS355). The interaction of dichlorocarbene, generated from chloroform and potassium hydroxide under phase-transfer conditions, with diazines affords the corresponding ylides; the latter react with dipolarophiles to give pyrrolodiazines (Scheme 20) (92MI3; 93S568).

Pyridinium ylides **90**, generated from chlorocarbenes and pyridine, produce [3 + 2]-cycloadducts with dimethyl acetylenedicarboxylate (88JA5595) and α -chloroacrylonitrile [89JCS(P1)1547]. The formation of azomethine ylide **91** from **92** and ethyl diazoacetate was postulated to explain the formation of adduct **93** [82JCS(P1)2169]. Several more examples are known of *N*-ylide generation by intermolecular addition of carbenoids from diazo acetophenone (93JOC1144) and ethyl diazomalonate (94JOC5347). The cycloaddition of these ylides to the corresponding dipolarophiles yields **94** and **95**.

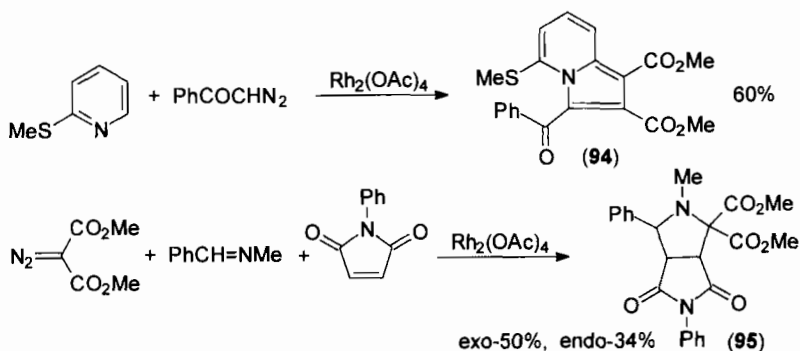
Molecular complexity greatly increases when an *N*-ylide is generated through intramolecular interaction of a carbene center with a nitrogen atom followed by 1,3-dipolar cycloaddition. This sequence allows the construction



a: pyridine; b: DMAD; c: H₂C=C(Cl)CN



R¹ = Me₂C=CCO₂Me, R² = PhCH₂, R³ = Me, Et; a: EtO₂CCHN₂, Cu(acac)₂

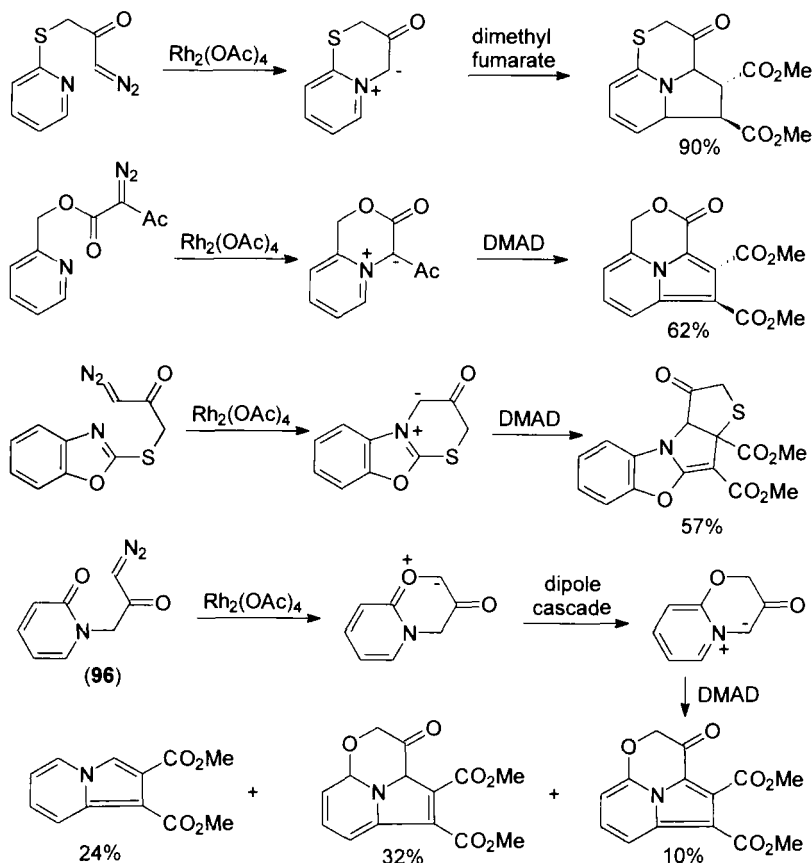


of two N-containing rings in one synthetic stage. Some examples are represented in Scheme 21 (93JOC1144).

The Rh(II)-catalyzed reaction of pyridone **96** with DMAD was also found to give cycloadducts derived from an intermediate azomethine ylide. The initial reaction involves generation of the expected carbonyl ylide by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the amide group. A subsequent proton shift generates the thermodynamically more stable azomethine ylide, which is trapped by DMAD. This is an example of subsequent formation of ylides of two types, a phenomenon termed a dipole cascade (93JOC1144).

Several more examples of the application of the dipole-cascade approach to five-membered nitrogen-containing rings from the work of Padwa and co-workers are shown in Scheme 22 (89JA6451; 92JA593, 92T7565).

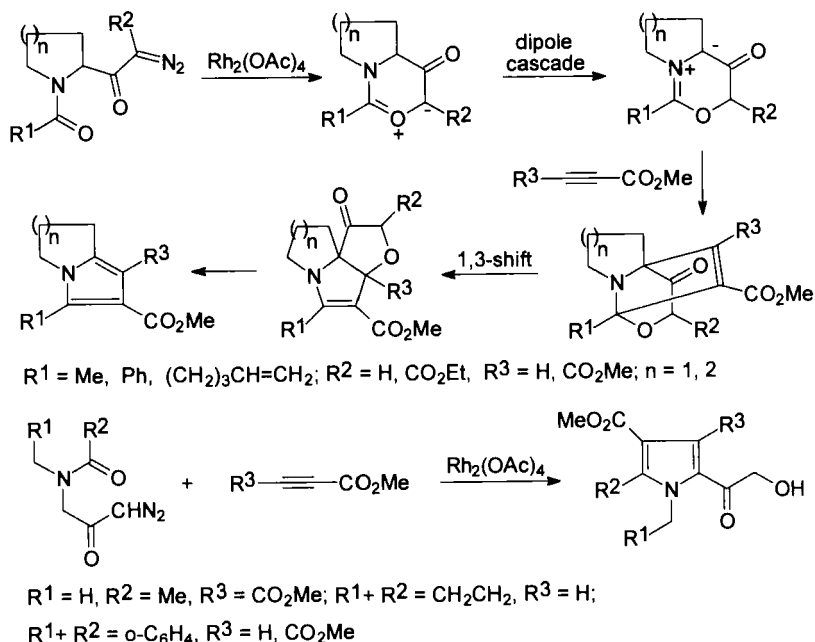
Reactions of carbenes with nitriles produce an intermediate nitrile ylide, which readily undergoes 1,3-dipolar cycloaddition. The formation of pyrro-



SCHEME 21

line **97** on thermolysis of diazo compound **98** in acrylonitrile was accounted for by addition of intermediate nitrile ylide **99** to the double bond of a second molecule of acrylonitrile (82JA4244). Photolysis of diazomethane or diazirine in acetonitrile in the presence of ethylenic and acetylenic dipolarophiles yields typical cycloadducts of nitrile ylide ($MeC\equiv N^+ - C^-H_2$), viz. pyrroles or pyrrolines (85JOC4415; 86JA6739). Similarly, 1,3-dipolar cycloaddition of a nitrile ylide, generated from 1-naphthyl carbene and acetonitrile, to acrylonitrile affords the corresponding pyrrolines (83TL3955; 86JA3928).

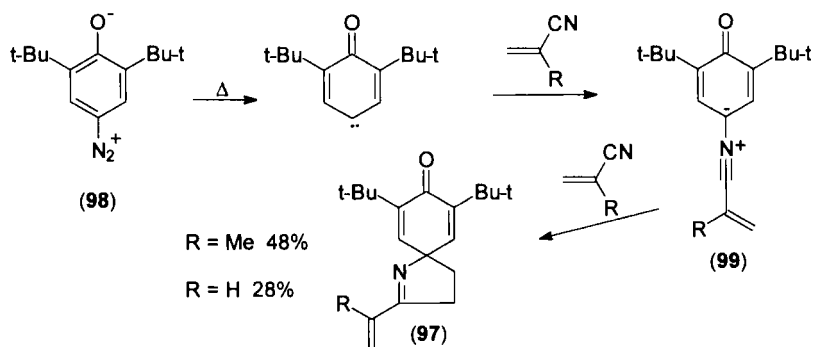
In some cases, nitrogen-containing carbenes, generated by thermolysis, give five-membered heterocycles as a result of a formal 1,3-dipolar cycloaddition (Scheme 23) [81AG(E)113; 85CB634].

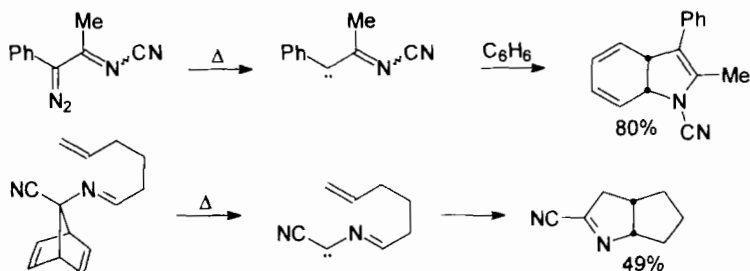


SCHEME 22

The synthesis of 3-substituted indolizine **100** is based on the reaction of chlorocarbenes with 2-vinylpyridine. Intramolecular 1,5-dipolar cyclization of intermediate pyridinium ylide **101** followed by hydrogen chloride elimination gives indolizine **100** [94CC509]. The formation of 3-chloroindolizine in a reaction with dichlorocarbene was detected previously [77ACS(B)224].

During short-term thermolysis conditions, nitrones **102** preferentially undergo monomolecular reactions leading to a product distribution that



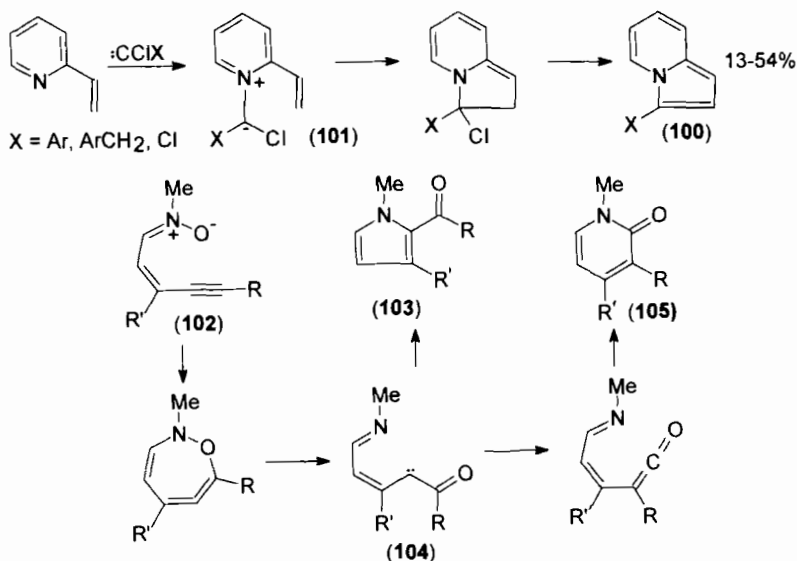


SCHEME 23

depends on the substituents of the dipole system. Nitron **102** ($R = R' = t\text{-Bu}$) transforms almost quantitatively to the pyrrole **103** ($R = R' = t\text{-Bu}$) via a 6π -cyclization of carbene **104** (87TL2689).

3. Intramolecular Cyclopropanation and Related Reactions

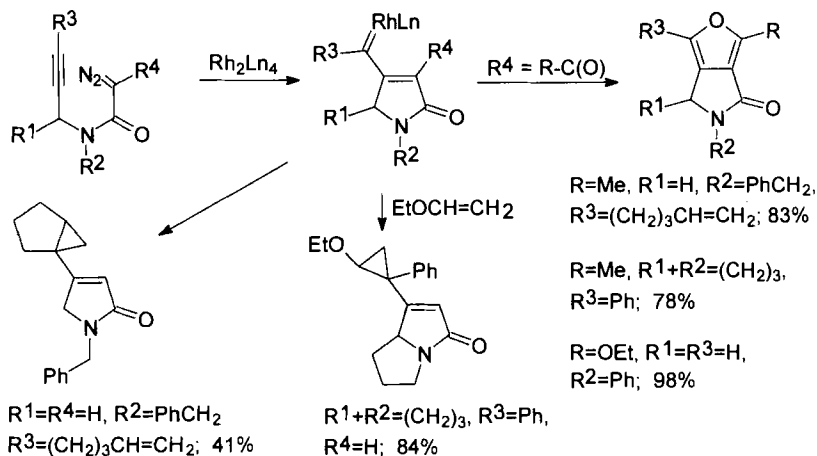
N-Alkynyl diazoacetamides and *N*-alkynyl malonamic esters, when treated with a catalytic quantity of Rh(II) catalyst, give furo[3,4-*c*]pyrroles in good yields. The reaction proceeds via addition of a rhodium(II)-stabilized carbenoid onto the acetylenic π -bond to give a vinyl carbenoid, which subsequently cyclizes onto the neighboring carbonyl group to produce the



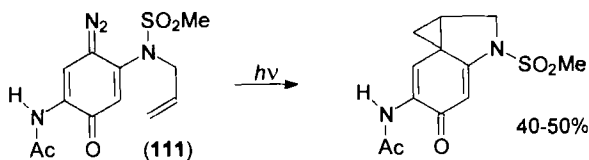
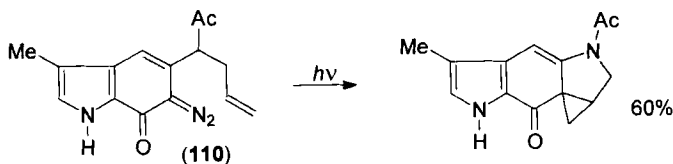
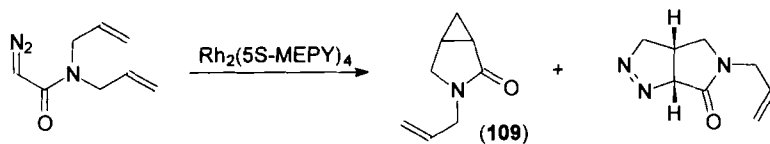
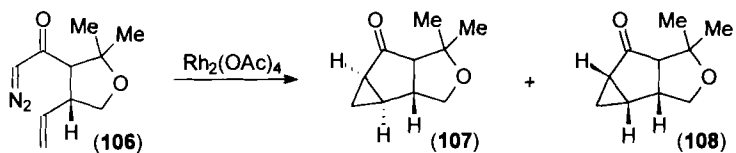
furan ring (Scheme 24) (93JOC4646; 94JOC2447). *N*-Alkynyl-substituted 2-diazoacetamides were found to cyclize onto the tethered alkyne unit. The resulting rhodium(II) carbenoid can undergo intra- and intermolecular cyclopropanation, depending on both electronic and conformational factors (Scheme 24) (93JOC4646).

An intramolecular carbenoid addition onto a carbon–carbon double bond provides a possible synthetic route to the pyrrolidine ring. The rhodium(II) acetate–catalyzed reaction of diazo amide **106** leads to a mixture of diastereomers **107** and **108** (6: 1) in 43% yield (88TL1181). The decomposition of *N,N*-diallyl- α -diazoacetamide catalyzed by $\text{Rh}_2(5\text{S-MEPY})_4$ forms product **109** from an enantioselective intramolecular cyclopropanation (50% yield, 72% e.e.) (94T1665). Spiro-fused ring systems were produced by this route from quinonediazides **110** and **111** under irradiation (83TL4773; 86TL2687).

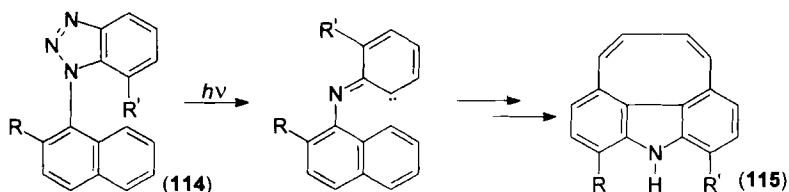
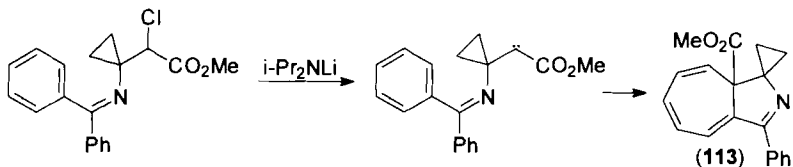
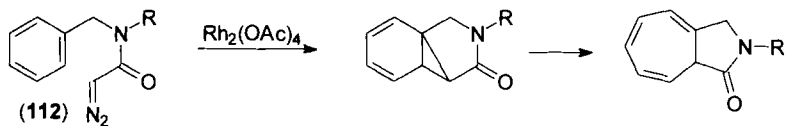
The process whereby carbenes or carbenoids add to an aromatic ring is commonly described as a cycloaddition reaction that forms a norcaradiene intermediate, which rearranges to a cycloheptatriene. Aromatic cycloaddition reactions are considered to be similar to cyclopropanation reactions of a C=C bond. Rhodium(II) acetate catalyzes high-yield intramolecular conversions of *N*-benzyldiazoacetamides **112** to azabicyclo[5.3.0]decatriones. When the aromatic ring contains a substituent at the 3-position, preferential addition occurs at the 1,6-position (88TL2639). The relative contribution of aromatic cycloaddition and C–H insertion is strongly catalyst- and temperature-dependent (93JA8669). Similarly, a 2-azaazulene derivative **113** was obtained in 70% yield, presumably via intramolecular cycloaddition of a carbene intermediate to the phenyl ring (90CC574).



SCHEME 24



Photolysis of benzotriazoles **114** was found to give cycloocta[*def*]carbazoles **115** as a result of cyclization of an imidoil carbene to the naphthalene 8a-position or cycloaddition to the naphthalene 8-8a bond with concomi-



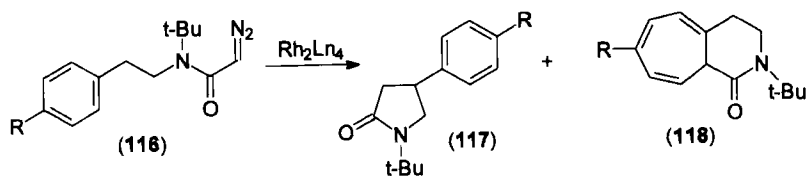
tant rearrangement. The highest yield (41%) is attained when $R = \text{Me}_3\text{Si}$ and $R' = \text{H}$ (87JCS(P1)403).

Decomposition of *N*-furfuryl-*N*-methyl diazoacetamide over a $\text{Rh}_2(\text{OAc})_4$ catalyst gives 3-(1-methyl-5-oxo-1,5-dihydropyrrol-3-yl) acrolein (14%), which appears to result from a consecutive carbenoid addition onto the $\text{C}=\text{C}$ bond of a furan ring and subsequent rearrangement (87HCA1429).

4. Intramolecular Aliphatic C—H Insertion Reactions

Intramolecular C—H insertion of carbenoids derived from diazoacetamides provides one of the most convenient routes to γ -lactams. However, synthetic application of this reaction may be restricted by the competitive formation of either β -lactams through aliphatic C—H insertion or δ -lactams through aromatic cycloaddition, etc. The competition between aromatic cycloaddition and C—H insertion is profoundly influenced by the choice of the dirhodium(II) ligand. With diazoacetamide **116** ($R = \text{H}$), $\text{Rh}_2(\text{cap})_4$ provides γ -lactam **117** ($R = \text{H}$) and virtually no **118** ($R = \text{H}$); but $\text{Rh}_2(\text{acam})_4$, like $\text{Rh}_2(\text{OAc})_4$, gives a mixture of the two products **117** and **118** ($R = \text{H}$). With the nitro derivative **116** ($R = \text{NO}_2$), use of $\text{Rh}_2(\text{acam})_4$ results in γ -lactam **117** ($R = \text{NO}_2$) in 90% yield (92JA1874; 93JA8669).

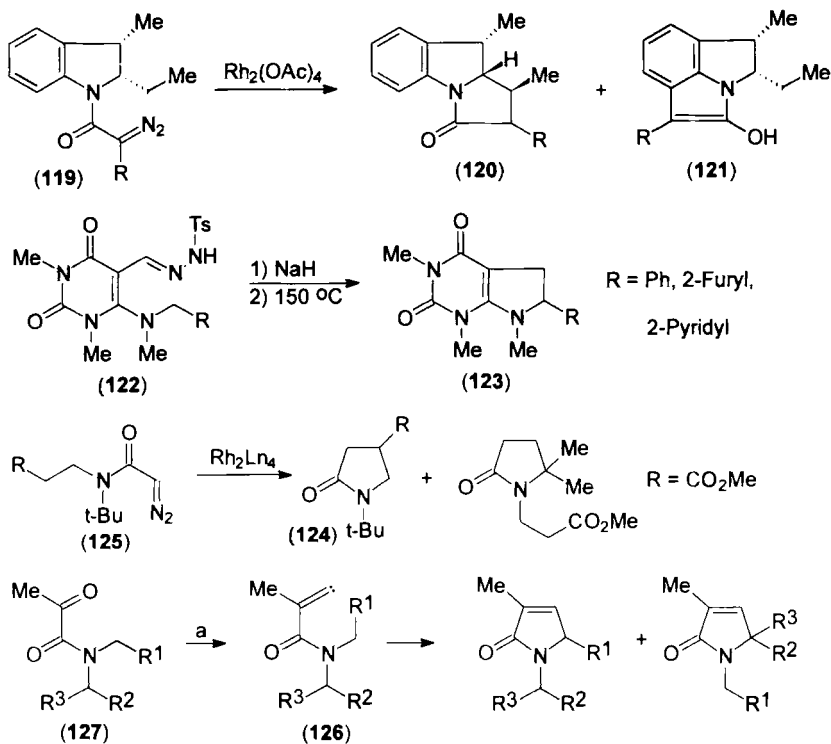
On passing from α -diazoacetamides **116** to the related α -acetyl- α -diazoacetamides **25** ($n = 1$), β -lactam formation becomes a major competing pathway, β - and γ -lactams **24** ($n = 1$) and **27** being isolated in comparable amounts regardless of the type of Rh(II) catalyst (93JA8669). The reaction selectivity is also substantially influenced by the nature of the substituent on the amide nitrogen in diazoacetamide. Thus, bulky substituents favor β -lactam formation [cf. **34** ($R = t\text{-Bu}$), Section III.B], while **34** ($R = \text{Pr}$, $R' = \text{Et}$) gives mostly γ -lactam **37** ($R' = \text{Et}$) (89TL5397; 91JOC820). Furthermore, the azabicyclo[4.1.0]heptane derivative, which might be formed via the intramolecular addition of the rhodium carbenoid onto the double bond of **41** ($n = 2$; $R^1 = 4\text{-MeOC}_6\text{H}_4$, $R^2 = \text{CH}=\text{CH}_2$, $R^3 = \text{Me}$), was not observed, whereas the insertion product into the allylic C—H bond, the corresponding γ -lactam **43**, was obtained in 81% yield (92JOC4404). Analogous results were encountered in the reaction of unsaturated diazoamides studied by Padwa and co-workers (93JOC4646).



The decomposition of **119** ($R = \text{Ac}$) gives the products of carbenoid aliphatic and aromatic C—H insertion, **120** ($R = \text{Ac}$) (61%) and **121** ($R = \text{Ac}$) (26%), respectively, while compound **119** with $R = \text{CO}_2\text{Me}$ or PhSO_2 gives the corresponding **120** in 99% yield (92JOC4404).

Insertion of a carbene into α -heteroatom-activated C—H bonds proceeds smoothly. The thermolysis of the sodium salts of tosylhydrazonouracil **122** gives pyrrolo[2,3-d]pyrimidines **123** in good yields (89H1993). The pyrrolidinone **124** ($R = \text{OEt}$) was obtained quantitatively as a result of carbenoid insertion into a C—H bond activated by an oxygen atom (92TL7819). Rhodium(II) catalysts possessing chiral pyrrolidone or oxazolidone ligands provide moderate enantiocontrol in C—H insertion reactions of diazo compound **125** ($R = \text{Et}$, *i*-Pr, OEt). Unprecedented insertion into an unactivated methyl C—H bond of the *tert*-butyl group of **125** ($R = \text{CO}_2\text{Me}$) occurs with a $\text{Rh}_2(\text{MEPY})_4$ catalyst (92TL7819).

Alkylidenecarbenes **126** give pyrrol-2-ones via intramolecular C—H insertion. As a synthetic method, the reaction is best suited for substrates in which the nitrogen of amides **127** is symmetrically substituted (86JOC3656).



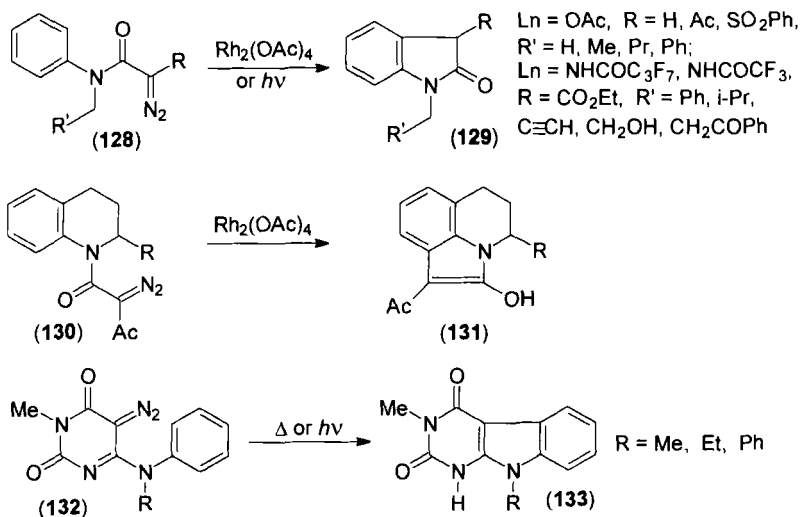
a: $(\text{EtO})_2\text{P}(\text{O})\text{CHN}_2$, *t*-BuOK, MeOH

5. Intramolecular Aromatic C—H Insertion Reactions

N-Aryldiazoacetamides **128** ($R = H$) and *N*-aryldiazoacetoacetamides **128** ($R = Ac$) undergo facile intramolecular aromatic substitution to form 2(3*H*)-indolinones (or 2-hydroxyindoles) **129** in 70–98% yield when these reactions are performed in the presence of a catalytic amount of $Rh_2(OAc)_4$ (88JOC1017; 92JOC4404). A *meta* methoxy or chloro substituent in the phenyl ring directs substitution solely to its *para* position, but a *meta* methyl substituent offers virtually no selectivity for substitution in the presence of $Rh_2(OAc)_4$ (90JOC1093). *N*- α -Naphthyldiazoacetamide undergoes exclusively intramolecular substitution at the β -position. The perfluoropolymeric sulfonic acid Nafion-H also catalyzes the decomposition of diazoacetanilides (88JOC1017). Photodecomposition of **128** ($R = H, Me, R' = H$) affords the corresponding oxindoles (81JOC1090).

A study of Rh_2Ln_4 -catalyzed decomposition of 2-diazo-*N*-phenylmalonic acid ethyl ester **128** ($R = CO_2Et$) showed, that with perfluorocarboxamides as catalyst ligands, the aromatic C—H insertion giving rise to oxindoles **129** occurs in preference to aliphatic C—H insertion, addition to $C=C$ and $C\equiv C$ bonds, O—H insertion, and ylide formation, all of which are observed simply by switching to a carboxylate-based rhodium catalyst (94JOC2447).

The rhodium(II) acetate-catalyzed reaction of diazo amide **130** ($R = H$) yields 42% of compound **131** ($R = H$) (90JOC1093). Quinoline **130** ($R =$

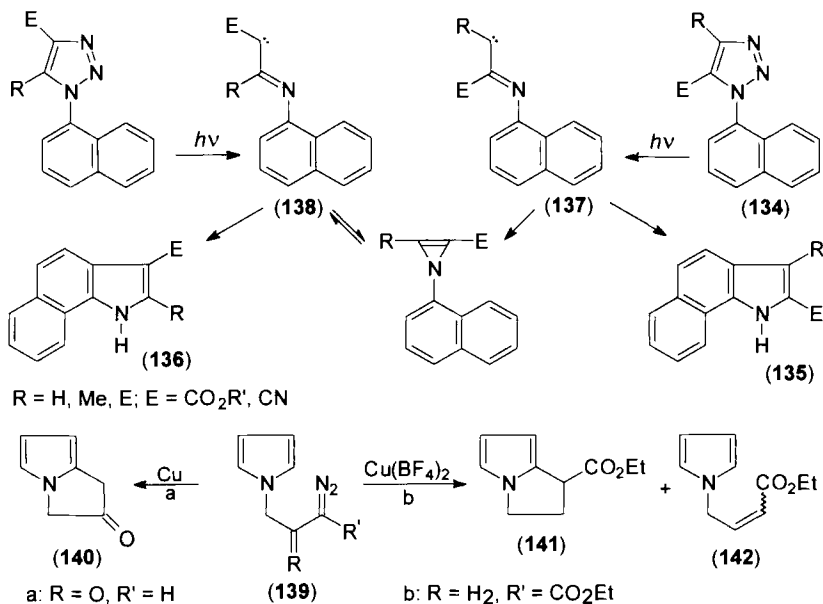


Et), unlike indole **119** ($R = \text{Ac}$), gives exclusively the aromatic C—H insertion product **131** ($R = \text{Et}$) in 88% yield. This difference is attributed to conformational effects about the amide N—C bond (92JOC4404).

Both photolysis and thermolysis of 5-diazouracils **132** result in the formation of formal aromatic C—H insertion products, the corresponding indolo[2,3-d]pyridines **133**, in good yields (77H1911).

High yields of benz[g]indoles were obtained from the photolysis of 1-(1-naphthyl)-1,2,3-triazoles when the triazole contained at least one electron-withdrawing group. Triazoles **134** with an electron-withdrawing group at C-5 give a mixture of the expected **135** and the rearranged indoles **136**. This is explained by a mechanism in which the less stable carbene intermediate **137** rearranges to the more stable carbene **138** via the 1*H*-azirine, in competition with its direct cyclization [87JCS(P1)413]. Photolysis of 1-phenyltriazoles follows the same pattern to provide indoles as a result of the aromatic C—H insertion of an intermediate carbene [86CC399; 87JCS(P1)413].

The copper-catalyzed pyrolysis of diazo ketone **139** ($R = \text{O}$, $R' = \text{H}$) gives pyrrolizine **140** in quantitative yield (83HCA2666). However, the decomposition of diazo ester **139** ($R = \text{H}_2$, $R' = \text{CO}_2\text{Et}$) is not preparatively useful, since a mixture of **141** and ester **142** was obtained in a yield of 35%, at best (83CJC454).



6. Miscellaneous Reactions

A series of substituted pyrroles was obtained in low yields upon treatment of cyclopropanes **143** with methyllithium. The mechanism is considered to involve the formation of iminocyclopropylidenes that undergo a carbene-carbene rearrangement to 2-azacyclopent-3-en-1-ylidenes, producing pyrroles via subsequent [1,2]-hydrogen migration [82TL113; 83JCR(S)100]. It is assumed (82TL113) that 1-hydroxy-2,3-dimethylpyrrole also results from the carbene-carbene rearrangement of [1-(1-methyl-2,2-dibromocyclopropyl)ethylidene]hydroxylamine (80TL2893).

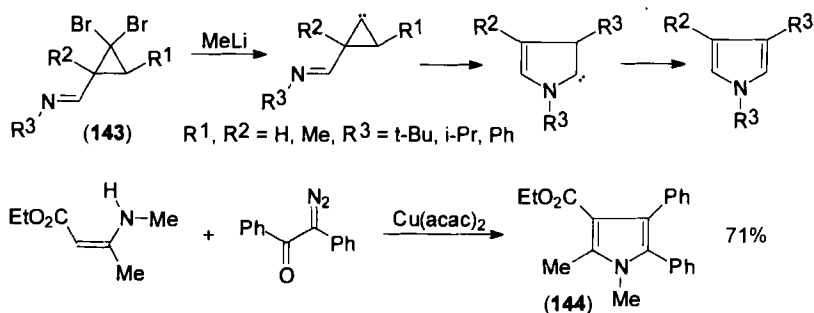
Carbenoids, derived from diazo ketones $\text{RCOCHN}_2\text{R}'$ ($\text{R} = \text{R}' = \text{Ph}$; $\text{R} = \text{Me}$, $\text{R}' = \text{Ph}$; $\text{R} = \text{Ph}$, $\text{R}' = \text{Me}$) react with enaminones to give pyrroles, e.g., **144**. The mechanism presumably involves the electrophilic attack of a keto carbenoid on N and/or at the C- α -position of an enaminone system, followed by cyclization and loss of water (88JOC2084).

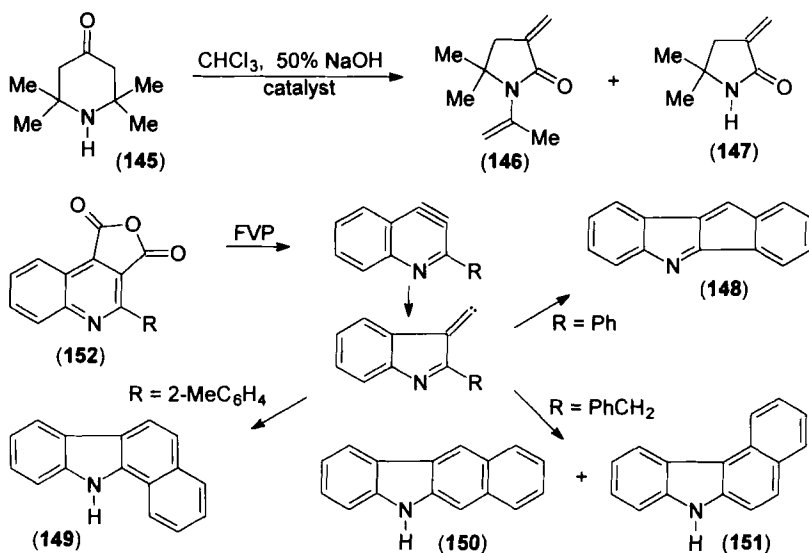
A number of nitrogen-containing five-membered heterocycles were synthesized through ring contraction accompanied by diverse carbene reactions whose mechanisms are not always well established.

Reaction of piperidone **145** with dichlorocarbene under phase-transfer catalysis conditions affords a mixture of **146** and **147** in 85–90% yields (80JOC1513, 80TL119) with the ratio determined by the catalyst (80JOC1513). The reaction presumably occurs via dichlorocarbene addition onto the carbonyl group of **145** followed by rearrangement with ring contraction.

The formation of indole **148** and carbazoles **149–151** upon flash vacuum pyrolysis (FVP) of anhydrides **152** can be explained in terms of the interception of a ring-contracted exocyclic carbene by the neighboring 2-aryl or 2-benzyl group (92T7763).

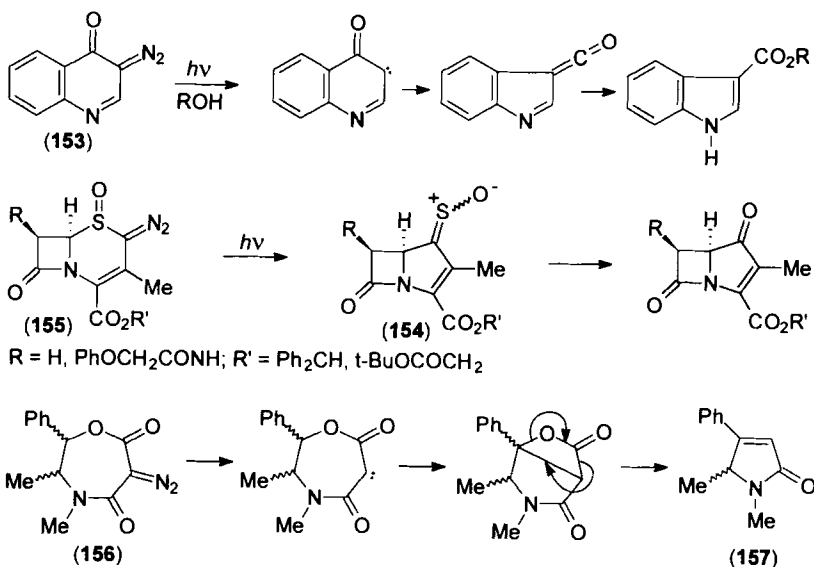
Irradiation of diazo quinoline **153** in alcohol provided the corresponding indole-3-carboxylic esters in 8–61% yield. Mechanistically, the transformation is a Wolff rearrangement and involves the formation of an intermediate carbene, ring contraction to ketene, and its solvolysis (76S754).





A Wolff-like mechanism involving the intermediacy of the sulfone **154** was proposed for conversion of cephalosporinates **155** to the corresponding carbapenems (82JA4262).

Ring contraction of **156** under cuprous triflate catalysis occurs stereoselectively to give either (*S*)- or (*R*)-pyrrolidones **157** in 95% yield (95AG104).



D. SIX-MEMBERED RINGS

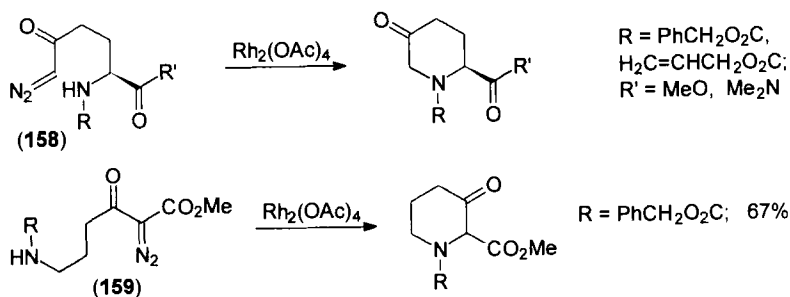
The set of carbene reactions providing access to six-membered nitrogen-containing rings is markedly different from that employed for preparing five-membered ones. The N—H insertion is still applicable, whereas the aliphatic C—H insertion is unsuitable by virtue of its kinetic preference for five-membered ring formation. The formal insertion into a C—H bond of pyrrole derivatives, however, offers a fruitful synthetic approach. This is also true for cyclizations involving *N*- and *S*-ylides followed by rearrangements. For six-membered rings, the most prominent synthetic significance is assumed by intramolecular cyclopropanation and ring expansion rather than ring-contraction reactions.

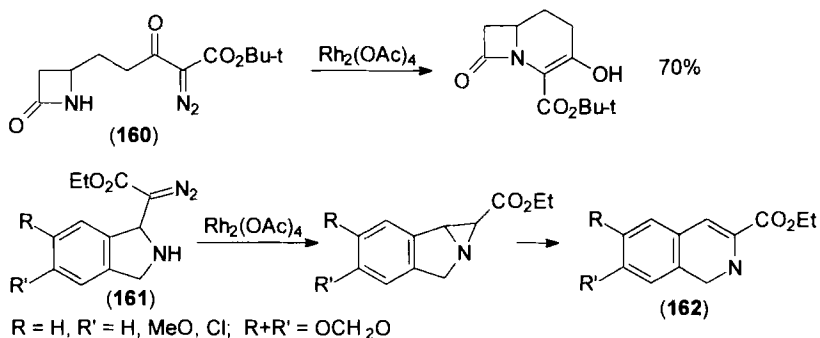
1. Intramolecular N—H Insertion Reactions

When a carbene center and a nitrogen are linked by a four-carbon chain, insertion into the N—H bond gives rise to piperidine derivatives. The rhodium(II) acetate-catalyzed decomposition of either diazo ketones **158** (92TL6651) or diazo ester **159** (85JOC5223) leads to insertion into the amide N—H bond to give products in moderate yields. Various solvents, temperatures, and catalyst concentrations were found to be important in determining the yield and the product distribution in the cyclization of **159**.

The ring-opening/cyclization sequence (Section III,C) has also been extended to the synthesis of protected 5-oxopipelic acid **61** ($n = 2$). Thus, when ylide **60** ($n = 2$) is treated with rhodium(II) trifluoroacetate, it affords 51% of **61** ($n = 1$) (93CC1434).

The intramolecular carbenoid insertion into the N—H bond of β -lactams is frequently used for constructing the 1-azabicyclo[4.2.0]octane ring system. Thus, in the synthesis of (–)-homothienamycin, the crucial ring closure was effected by refluxing compound **160** in a benzene solution containing $\text{Rh}_2(\text{OAc})_4$ (80TL1193). Such an approach was used to advantage in





the enantioselective synthesis of some carbacephalosporins (85TL3787; 89TL2321).

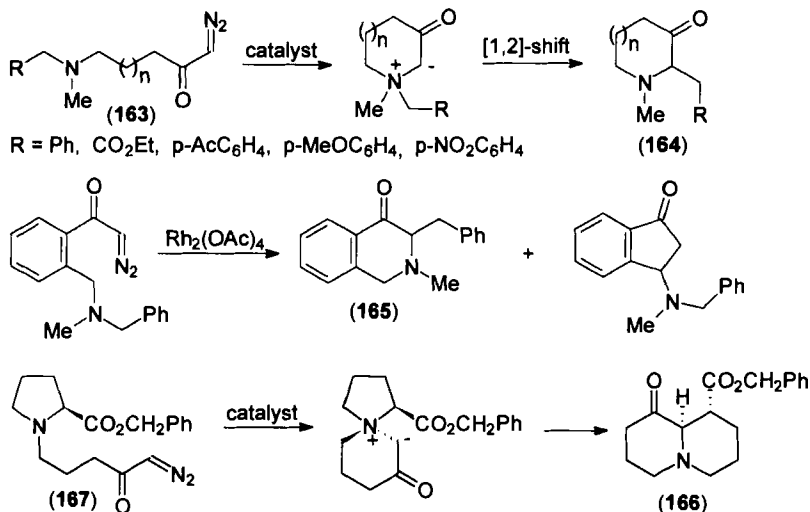
Treatment of diazo compounds **161** with $\text{Rh}_2(\text{OAc})_4$ affords 1,2-dihydro-isouquinolines **162** in 37–66% yield. The reaction presumably involves ring expansion in aziridine intermediates which are likely to be formed through carbenoid insertion into the N–H bond (84H2571; 86JOC1120).

2. Ylide Formation and Subsequent Reactions

A further route to six-membered nitrogenous rings consists in carbenoid-mediated cyclic ammonium ylide formation in conjunction with the Stevens [1,2]-shift. Treatment of diazo ketones **163** with $\text{Rh}_2(\text{OAc})_4$ affords piperidines **164** in 56–99% yield. Introduction of an *ortho* phenylene unit between the nitrogen and the diazocarbonyl moiety reduces the yield of the transformation product **165** to 44%, a considerable amount of C–H insertion product being formed (93JA1177). When $\text{Cu}(\text{acac})_2$ is substituted for $\text{Rh}_2(\text{OAc})_4$, the yield of piperidine **164** ($n = 1$; $\text{R} = \text{Ph}$) falls from 99 to 69% (94JOC6892). The potential of the three-step carbenoid generation/ammonium ylide formation/[1,2]-shift method for the efficient construction of polycyclic alkaloid skeletons was demonstrated by the synthesis of (–)-epilupinine. The key intermediate **166** was obtained by treatment of **167** with $\text{Cu}(\text{acac})_2$ in 84% yield and 75% e.e.; with $\text{Rh}_2(\text{OAc})_4$, the reaction is less stereoselective (94JA8420).

Carbenoid generation/ammonium ylide formation/[2,3]-shift methodology is also a suitable synthetic route to piperidones. Thus, piperidone **68** ($n = 2$; $\text{R} = \text{c-C}_3\text{H}_5$) was obtained in 79% yield (94CC2701).

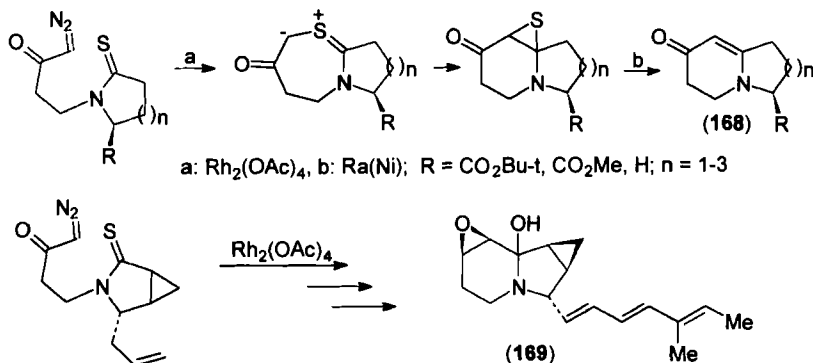
One more approach to producing six-membered N-containing rings involves thiocarbonyl ylide formation through reaction of a carbenoid with the thiolactam sulfur atom. In this case, the initially formed ylides cyclize to the corresponding episulfides. The latter compounds, through consecutive

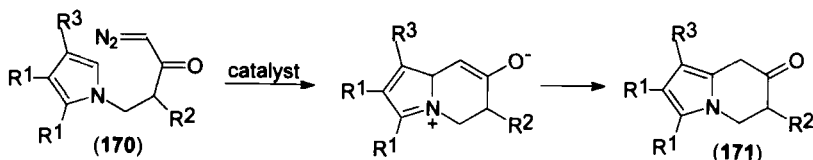


isomerization and Raney nickel desulfurization, were converted to **168** in 65–73% yield (89TL3625). This reaction sequence was applied to the synthesis of indolizomycin **169** (90JA2003).

3. Intramolecular C—H Insertion Reactions

Intramolecular aliphatic C—H insertion is synthetically impractical with piperidine derivatives. However, formal insertion into the C—H bond of the pyrrole ring is of synthetic utility with indolizine derivatives. The copper-catalyzed pyrolysis of **170** ($\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$) quantitatively gives indolizone **171** ($\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$). The insertion of a strongly electrophilic





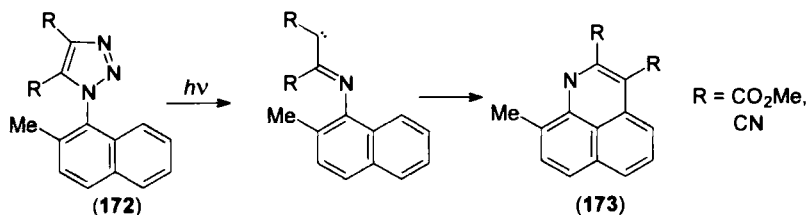
carbenoid, arising from **170** ($R^1 = R^2 = R^3 = H$) at the α -position of the pyrrole ring followed by proton transfer, accounts for the observed product. Pyrolysis of diazo ketone **170** ($R^1 + R^1 = (CH=CH)_2$, $R^2 = H$, $R^3 = Me$) was less efficient, giving the corresponding benzoindolizine **171** in just 7% yield. The failure of diazo ketone **170** to cyclize in a satisfactory yield was attributed to the diminished nucleophilic character at the α -position of the indole nucleus (83HCA2666). If the molecule of **170** ($R^1 = R^2 = H$, $R^3 = Ar$) contains an electron-rich phenyl ring, a minor amount of phenyl insertion product, the corresponding 1-(pyrrol-1-ylmethyl)indan-2-one, is formed together with **171**, whereas **170** ($R^1 = R^2 = H$, $R^3 = p\text{-NO}_2\text{C}_6\text{H}_4$) gives exclusively **171** in 76% yield (85TL6035; 86HCA2048).

The above approach, with $\text{Rh}_2(\text{OAc})_4$ as a catalyst, was applied to the synthesis of (\pm)-monomorine (89HCA1749; 91JA3513) and indolizines **167B** and **209D** (91JA3513; 93TL3119).

Photolysis of triazoles **172** ($R = \text{CO}_2\text{Me}$, CN) affords the corresponding quinolines **175** (65 and 74%, respectively). In this case, instead of an electrocyclization like that proposed above for the naphthyltriazoles **134** lacking the blocking 2-methyl group, the carbene attacks the naphthalene 8-position, inserting into the C—H bond [87JCS(P1)413].

4. Intramolecular Cyclopropanation Reactions

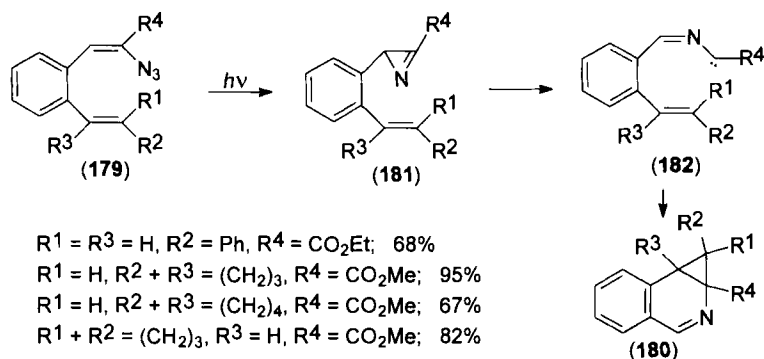
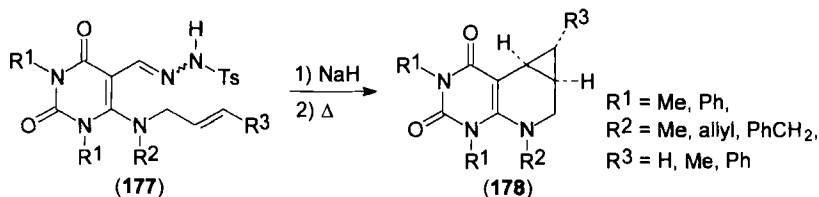
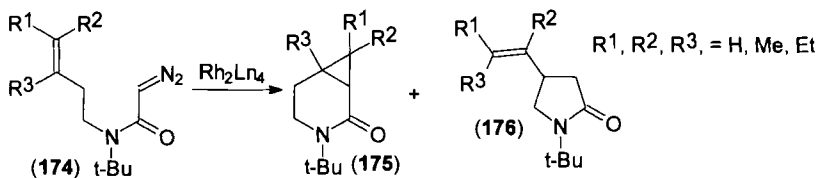
Intramolecular cyclopropanation is used to advantage for the preparation of cyclopropa[b]/[c]pyridine derivatives. Decomposition of diazoacetamides **174** catalyzed by $\text{Rh}_2(5S\text{-MEPY})_4$ and $\text{Rh}_2(4S\text{-MEOX})_4$ affords **175**, the products of intramolecular carbenoid addition onto the $\text{C}=\text{C}$



bond, in good yields with enantiomeric excess ranging from 60 to 90%. Competition from insertion into the allylic C—H bond to produce compounds **176** is of minor importance except in reactions with **174** ($R^1 = \text{Et}$, $R^2 = R^3 = \text{H}$), where the **175**:**176** product ratio is about 6:4 (94TL1665).

Intramolecular [2+1]-cycloaddition of the carbene generated by pyrolysis of the sodium salt of **177** affords **178** in 58–93% yield (89H1993). Photolysis of azidocinnamates **179** gives cyclopropaisoquinolines **180** [86JCS(P1)1119], including polycyclic [86JCS(P1)1123] and spirocyclic [87JCS(P1)913] forms. Their formation was rationalized in terms of photochemical ring opening of azirine intermediates **181** to iminocarbenes **182**, which are then intercepted intramolecularly. Iminocarbenes, generated by the 1,3-dehydrochlorination of *N*-(2-alkenylbenzyl)benzimidoyl chlorides using potassium *tert*-butoxide as base, cyclize at room temperature to give cyclopropa[*c*]isoquinolines **180** ($R^1 = R^2 = \text{H}$, Me, Ph; $R^3 = \text{H}$, $R^4 = \text{Ph}$) in 56–91% yield [92JCS(P1)1709].

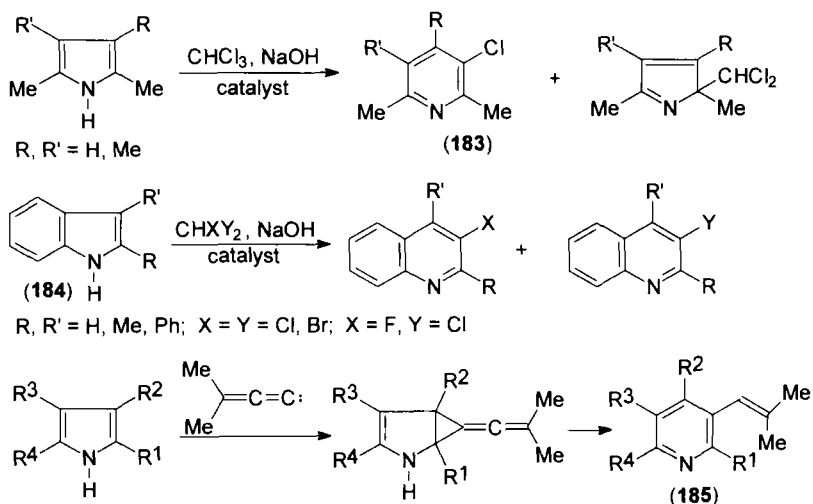
Intramolecular cyclopropanation of an aromatic ring, accompanied by rearrangement to cycloheptatriene, can be used to produce the 9-



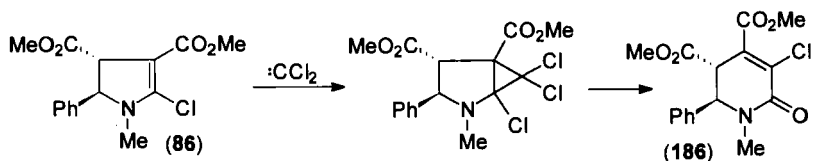
azabicyclo[5.4.0]undecane ring system. Chemoselective decomposition of diazoacetamides **116** ($R = H, MeO$) (aromatic cycloaddition versus aliphatic $C-H$ insertion) is achievable by changing the rhodium(II) ligands. Thus, with $Rh_2(pfb)_4$ the corresponding compounds **118** were formed nearly exclusively (92JA1874; 93JA8669).

5. Ring-Expansion Reactions

Pyrrole derivatives react intermolecularly with carbenes to afford six-membered rings. Although the ring expansion of pyrroles and indoles into 3-halogenopyridines and 3-halogenoquinolines by the reaction with dihalogenocarbenes has been intensively investigated for a long time (for reviews, see, e.g., 76KGS1443; 83KGS723), this reaction has limited synthetic value because of its low yield. However, the use of phase-transfer catalysts for dihalogenocarbene generation offers a significant improvement in the yield while simplifying the procedure. The reaction of dichlorocarbene with pyrroles under phase-transfer conditions results in 3-chloropyridines **183** in 40–50% yield (76S798). Under the same conditions, indoles **184** with dichloro-, dibromo-, and chlorofluorocarbenes give 3-chloroquinoline (45–68%) (76S249, 76S798), 3-bromoquinoline (24–37%) (76S249), and 3-fluoroquinoline (6–30%) (79LA1456), respectively. The reaction of pyrroles and indoles with dichlorocarbenes generated by pyrolysis of chloroform at 550°C leads to the formation of the corresponding 3-chloropyridines and -quinolines as the major products and to the corresponding 2-chloro



R¹, R², R³, R⁴ = H, Me; R¹+R¹ = (CH=CH)₂



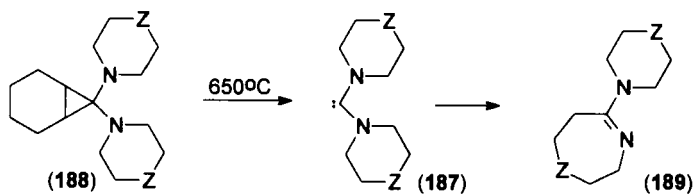
derivatives as the minor products [79JCS(P1)1578, 79JCS(P1)2782]. With PhHgCCl₂F as the source of chlorofluorocarbene, a 50% yield of 2,4-dimethyl-3-fluoroquinoline was obtained (83G129). Electrogenenerated dichlorocarbene gives 3-chloro-2,4-dimethylquinoline in 13–16% yield (95JOC445).

Allenic carbenes react with methylpyrroles and indoles to give 3-alkenyl pyridines **185** [87JCS(P1)1347] and quinolines **185** [R³+R⁴ = (CH=CH)₂] [76JCS(P1)2103] in low yield.

2-Chloropyrroline **86**, arising from the reaction of imine **85** (R = Me) with dichlorocarbene and dimethyl maleate, with an excess of dichlorocarbene, gives pyridine **186** (40% per imine) [91MI1, 95ZOR(ip)]. Pyridine derivatives are also formed in the reaction of ketene imines with dichlorocarbene and activated ethylenes (see Scheme 19) (87KGS1336; 88ZOR-1917).

Diaminocarbene **187** generated by flash vacuum pyrolysis of 7,7-dipyrroli-dinonorcaradiene **188** (Z = bond) is stabilized by an insertion reaction into the heterocyclic system to give tetrahydropyridine **189** (Z = bond) (88JOC1806).

We also note that pyrolysis of nitron **102** (R = H, R' = Me) occurs through a sequence of rearrangements involving carbene, resulting in the formation of pyridine **105** (R = H, R' = Me) in 77% yield. Nitron **102** (R = R' = Me) gives a mixture of pyridine **105** (R = R' = Me), 3-acetyl-1,2-dimethylpyrrole, and 4-acetylpyridine (33, 5, and 5%, respectively) (87TL2689).



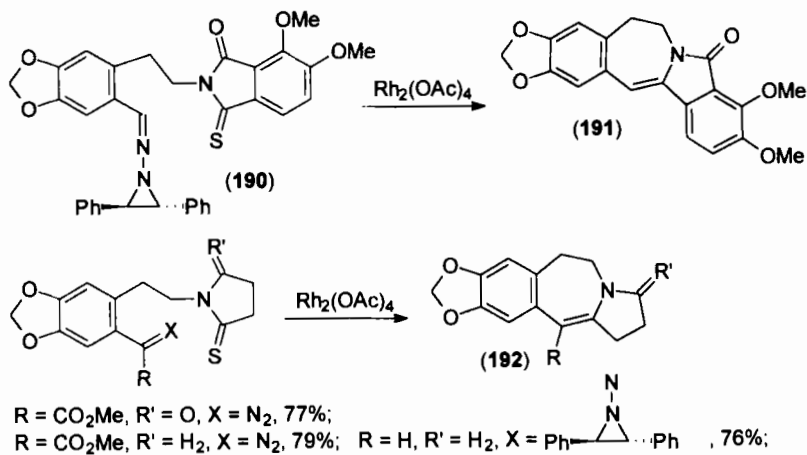
E. OTHER RINGS WITH ONE NITROGEN ATOM

Carbene reactions giving rise to seven-membered rings incorporating a nitrogen atom generally occur with the participation of the heteroatom.

Rhodium(II) acetate-mediated reductive coupling of 2,3-diphenyl-*N*-aziridinohydrazone and dimethoxyphthalimide units of **190** provides the key step in the total synthesis of the alkaloid chilepine. Addition of **190** to a refluxing suspension of $\text{Rh}_2(\text{OAc})_4$ in toluene generates a carbenoid, which cyclizes to a thiocarbonyl ylide, undergoing subsequent rearrangement and desulfurization to afford **191** (78%) (89TL2747). This methodology proved to be very suitable for constructing the pyrrolobenzazepine structures **192** (90JOC831).

Attempts to apply Rh(II)-catalysis conditions similar to those in the synthesis of piperidones **164** ($n = 1$) to substrates **163** ($n = 2, 3$; $\text{R} = \text{Ph}$) with one or two additional methylene units in the linker met with little success [**164** ($n = 2$; $\text{R} = \text{Ph}$) 35% yield, ($n = 3$; $\text{R} = \text{Ph}$) 0% yield]. Intramolecular C—H insertion to give cyclopentanones appeared to be the major pathway in these cases. Use of $\text{Cu}(\text{acac})_2$ -catalyzed decomposition of **163** ($n = 2, 3$; $\text{R} = \text{Ph}$) furnishes **164** ($n = 2, 3$; $\text{R} = \text{Ph}$) in 61 and 58% yield, suggesting a remarkably efficient and selective capture of the copper carbenoid by the amine to give a medium-size cyclic ylide in preference to other carbenoid pathways (94JOC6892).

The attempted synthesis of the corresponding azepinone under $\text{Rh}_2(\text{OAc})_4$ -catalyzed decomposition of $\text{RNH}(\text{CH}_2)_4\text{COCN}_2\text{CO}_2\text{Et}$ ($\text{R} = \text{PhCH}_2\text{OCO}$) (85JOC5223) or ($\text{R} = \text{Boc}$) (87TL5351) has failed, resulting in C—H, rather than N—H insertion products.



The rearrangement of dipiperidinocarbene **187** ($Z = \text{CH}_2$) generated by cycloelimination of aminocyclopropane derivative **188** ($Z = \text{CH}_2$) produces tetrahydroazepine **189** ($Z \approx \text{CH}_2$) in 84% yield (88JOC1806).

Tandem intramolecular ylide formation and [2,3]-sigmatropic rearrangement from copper carbenoids is a useful method for preparing seven- and eight-membered cyclic amines **68** ($n = 3$, $R = \text{Me}$; $n = 4$, $R = \textit{c}$ - C_3H_5). The rhodium(II) acetate-catalyzed reaction is less effective (94CC2701).

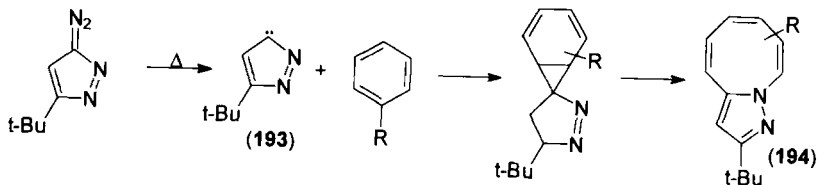
An azocine ring is seldom formed in carbene reactions. In addition to the above-mentioned formation of azocines **164** ($n = 3$) and **68** ($n = 4$), the conversions of benzenes by 5-*tert*-butyl-3*H*-pyrazolidene (**193**) to pyrazolo[1,5-*a*]azocines **194**, have been reported—the highest yield (40%) being attained with nitrobenzene (79TL4697).

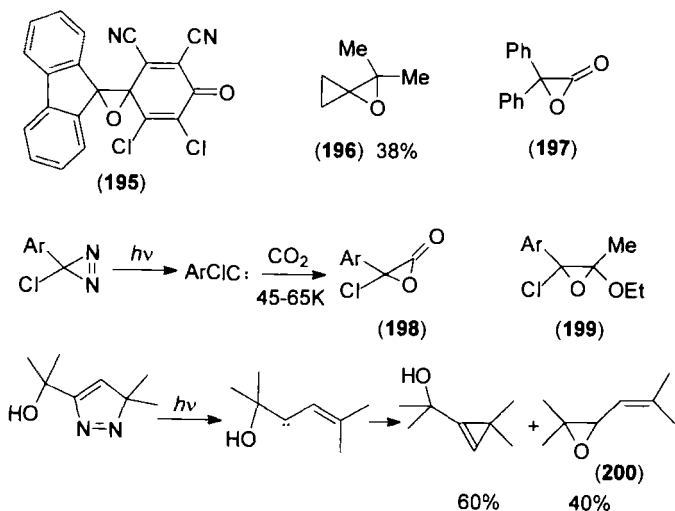
IV. Synthesis of Rings with One Oxygen Atom

A. THREE-MEMBERED RINGS

Carbene reactions with a $\text{C}=\text{O}$ bond leading to oxiranes involve carbonyl ylides formation and their subsequent reversible 1,3-cyclization (82JA4953; 83JOC1898; 94T7435). Because some oxiranes are unstable and very reactive, they can be used in a variety of subsequent heterocyclizations. The reaction of 9-diazofluorene with 2,3-dichloro-5,6-dicyanobenzoquinone in acetonitrile gives oxirane **195** in 93% yield [82JA6631; 85JA(107)7204; 86CL1639]. Cyclopropylidene, generated from a suitable diazo compound, adds to the multiple bond of ketones to form oxaspiropentanes **196** (86CB1511). Diphenylcarbene and arylchlorocarbene in an argon matrix at $10\text{--}45^\circ\text{C}$ react with carbon dioxide to produce α -lactones **197** (89JOC4265) and **198** (92JOC1051), respectively. Ethyl acetate in this reaction also yields oxirane **199** (91JA6585).

Vinylcarbene, generated by photolysis of substituted pyrazolenine, affords a mixture of the cyclopropene derivative and vinyloxirane **200** via insertion into an α -hydroxy group [66JCS(C)1719]. Phenylloxiranes

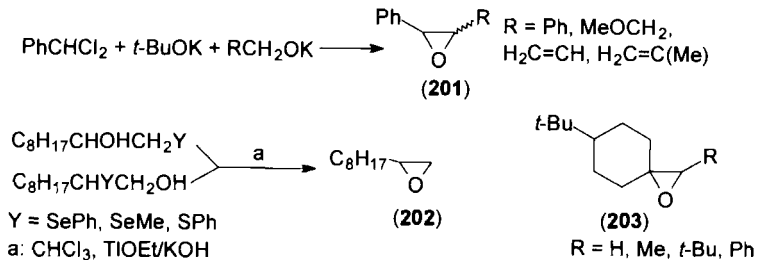


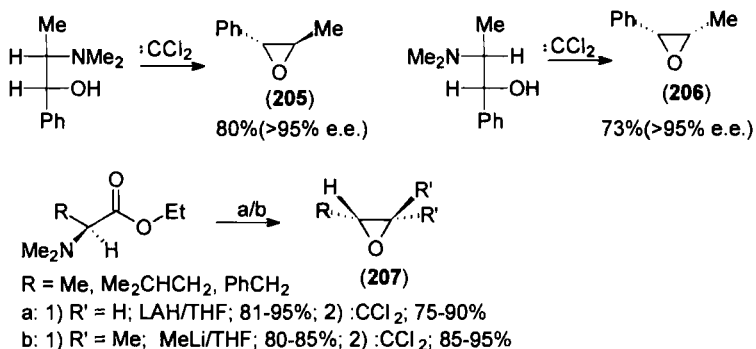


have also been detected in the photolysis of β -diazo- β -phenylethanol (90CC1243).

Oxiranes **201** have been obtained in 66–79% yields as an equimolar mixture of *cis* and *trans* isomers in the reaction of alkoxide anions with phenylchlorocarbene generated from benzal chloride and potassium *tert*-butoxide (83JA2771).

Dichlorocarbene reacts with alcohols bearing vicinal dimethylamino, phenylthio, or phenylseleno groups, giving oxiranes in good yields, e.g., **202** (42–74%) and **203** (42–90%) (84TL4569). Mechanistically, the reaction includes *N*-, *S*- or *Se*-ylide (**204**) formation and their subsequent transformation to oxiranes through intramolecular substitution, as shown in Scheme 25. It is clearly possible that an ylide may act as an internal base to promote an intramolecular deprotonation. 1,3-Cyclization occurs *trans* stereospecifically, and this peculiarity has allowed the synthesis of chiral oxiranes





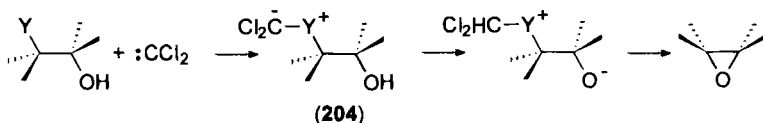
205, **206**, and **207** with complete enantioselectivity from optically active amino alcohols (82H209; 90TL4573) or esters of amino acids (84TL1205).

Decomposition of α -diazo ketoamides **208** in the presence of substituted propiolic esters gives spirocyclic oxiranes **209**. The reaction involves intramolecular addition of a rhodium carbenoid onto the oxygen atom of the amide group to yield the carbonyl ylide, which, after 1,4-H-migration, produces a cyclic ketene *N,O*-acetal **210**. The latter further reacts with the activated triple bond of the dipolarophile to form a zwitterionic intermediate and, finally, a spirocycloadduct (Scheme 26) (90JA2037).

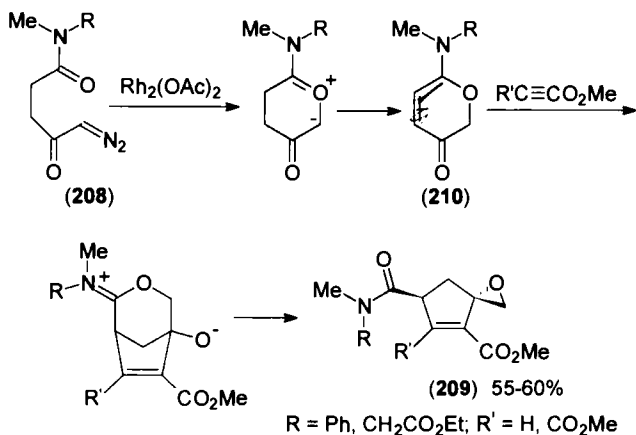
B. FOUR-MEMBERED RINGS

Photolytic and catalytic decomposition of α -diazo esters produces β -lactones, which are formed via intramolecular C—H insertion of a carbene or carbenoids. Tertiary alkyl esters of diazomalonate are decomposed by rhodium acetate with exclusive formation of the four-membered ring **211**. This suggests a smooth insertion into the C—H bond activated by the adjacent oxygen atom (90TL1023). β -Lactone **212** was obtained by photolysis of diazo malonic ester **213** (71CC577).

Benzoxetanes **214** were observed among the photolysis products of diaryldiazomethanes containing an *ortho* hydroxy group [91JCS(P1)471]. Substituted oxetane carboxylic acid **215** was first synthesized in preparative



SCHEME 25



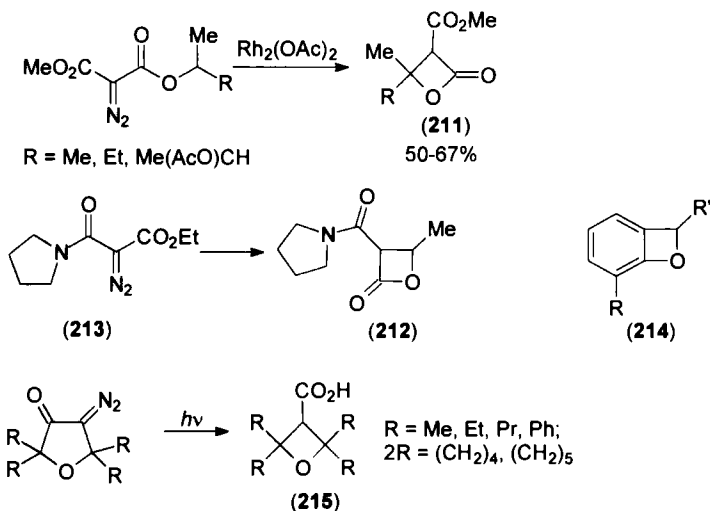
SCHEME 26

yields (47–97%) through the Wolff rearrangement of 4-diazo tetraalkyl-3-furanidones (68ZOR2016).

C. FIVE-MEMBERED RINGS

1. Intramolecular Insertion Reactions

An oxolane ring is readily available through an intramolecular reaction of a carbene or carbenoid with an oxygen atom or a C—H bond, particularly

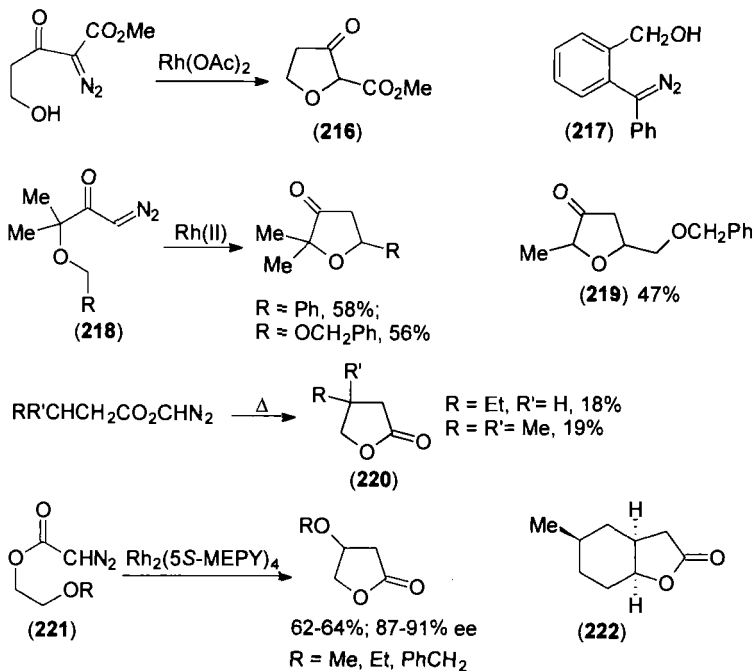


when the latter is positioned α with respect to the oxygen. The reaction primarily involves oxonium ylide formation, which is followed by a sigma-tropic shift resulting in the insertion product.

The intramolecular O—H insertion reaction of a carbene has been successful in the synthesis of the oxygen-containing heterocycle **216** in quantitative yield (85JOC5223). Carbene generated by photolysis of diazo precursor **217** in protic solvents gives 2-phenyl-2,5-dihydroisobenzofuran competitively with insertion into the O—H bonds of the solvent (90JOC2325).

Treatment of the alkoxy diazoketones **218** with rhodium(II) acetate affords 3(2*H*)-furanones in suitable yields (89TL1749). The carbenoid cyclization reaction to form 2,5-disubstituted 3(2*H*)-furanones exhibits a stereoselection favoring the *cis* isomers. This phenomenon was exploited in an enantioselective synthesis of (+)-muscarine (89TL1753). The formation of furanone **219** illustrates the clear preference for the five-membered ring when two ether oxygens are present to activate the C—H bonds, leading to either the five- or six-membered rings.

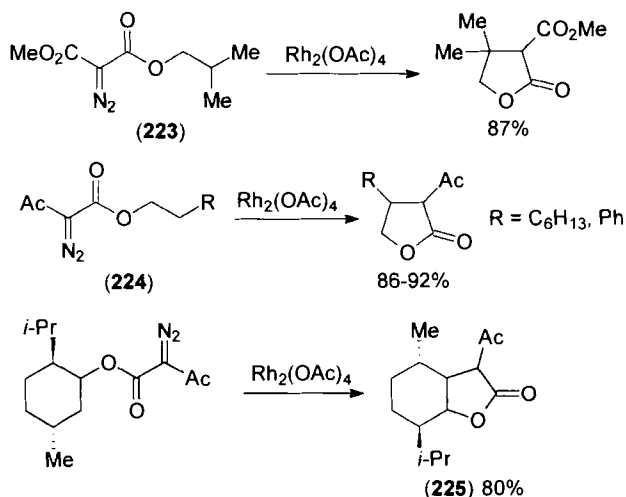
Gas-phase pyrolysis of diazoacetic esters affords γ -butyrolactones **220** in moderate yields (79IZV1652). Using Rh(II) catalysts ensures greater yields of lactones and allows the reactions to be carried out in methylene chloride

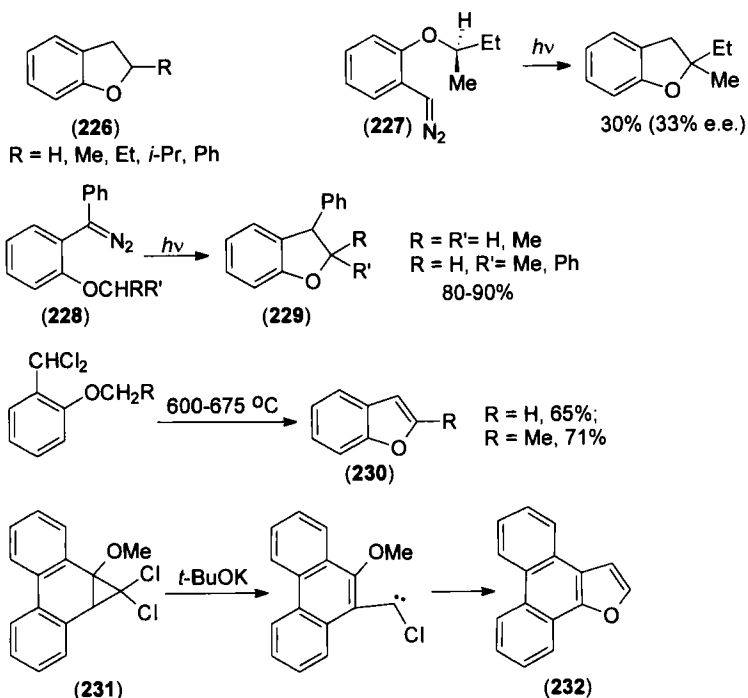


at room temperature. Rhodium(II) acetamide-catalyzed decomposition of diazo esters forms γ -lactones in high yield and occurs with exceptionally high regio- and diastereoselectivity (89TL7001). Enantiocontrol has recently been achieved with selected substrates **221** through the use of chiral rhodium carboxamides or homochiral carboxylates (90TL5173; 91JA8982). Diazo decomposition of cyclohexyl diazoacetate by chiral catalyst $\text{Rh}_2(4\text{S-MACIM})_4$ results in the formation of *cis*-fused bicyclic lactone **222** in 99:1 excess over the *trans* isomer and with 97% e.e. With $\text{Rh}_2(\text{MEPY})_4$ and $\text{Rh}_2(\text{MEOX})_4$ catalysts, the dominant selectivity is for the *trans* ring-fused product (94JA4507).

Diazomalonates **223** (90TL1023) or diazoacetoacetates **224** (93JA958) with an alkoxy group containing a secondary or tertiary $\varepsilon\text{-C-H}$ bond decompose with a Rh(II) catalyst leading to γ -lactones in good yield. $\text{Rh}_2(\text{OAc})_4$ -catalyzed decomposition of (1*R*,2*S*,5*R*)-(-)-menthyl diazoacetoacetate results in the exclusive formation of bicyclic γ -lactone **225** in 80% yield by insertion into a secondary C-H bond with no evidence of reaction with a tertiary C-H bond (89TL7001; 93JA958).

(*p*-Methoxyphenyl)carbene, generated by photolysis of a corresponding diazomethane (93JA792) or by pyrolysis of trimethylsilyl-(*o*-methoxyphenyl)methanol at 600°C (80JOC5286), gives 2,3-dihydrobenzofuran **226** (*R* = H). Photolysis of (*o*-alkoxyphenyl)diazomethanes leads to 2-substituted derivatives **226** (79AJC99; 93JA792). For ether **227** containing an alkyl group with an asymmetric center, the reaction takes a radical pathway and is therefore poorly stereoselective (92JA7590). Irradiation of 2-alkoxydiphenyldiazomethanes **228** produces dihydrobenzofurans **229** in good yield,





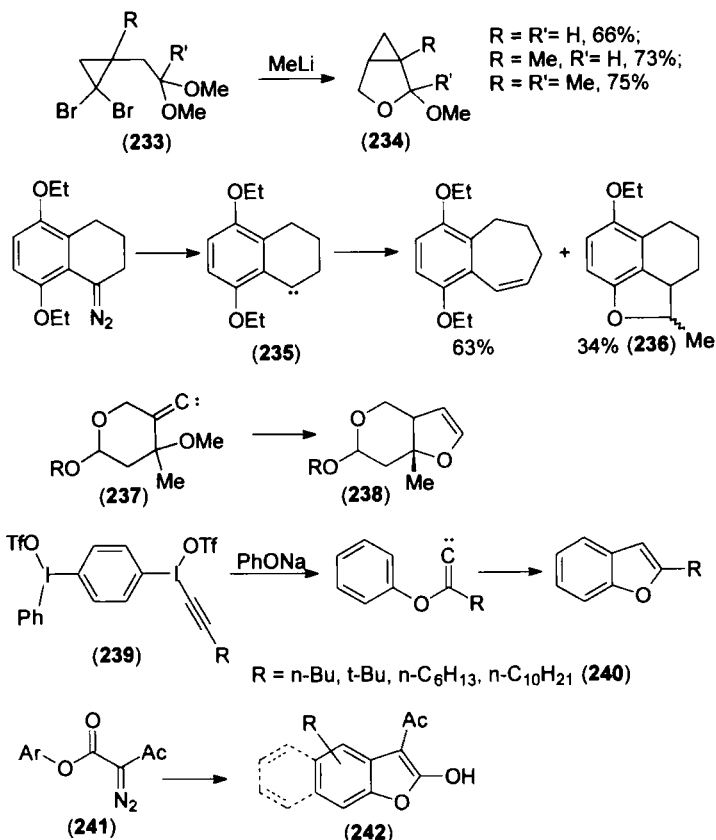
presumably as a result of intramolecular C—H insertion of carbenes [91JCS(P1)465, 91JCS(P1)471].

Flash vacuum pyrolysis of *o*-alkoxybenzylidene chlorides gives benzofurans **230**, which is consistent with intermediate carbene formation followed by intramolecular α -C—H insertion and elimination of hydrogen chloride (83TL609).

When the dichlorocarbene adduct **231** of 9-methoxyphenanthrene is reacted with 2 equivalents of *t*-BuOK in tetrahydrofuran in the presence of a crown ether, the phenanthro[9,10-*b*]furan **232** is obtained in 80% yield. The intermediate methoxy-substituted chlorocarbene is derived from cyclopropene. The key step consists in an intramolecular carbene insertion into the C—H bond of the methoxy group (84C79).

Cyclopropylidenes derived from acetyl- or formyl-*gem*-dibromocyclopropane dimethylacetals **233** and methyl lithium insert into the α -C—H bond of an alkyl group to produce bicyclic products **234** [83ACS(B)681; 88ACS(B)475].

A series of benzo-fused cyclic carbenes **235** bearing alkoxy substituents in the phenyl ring was generated in the gas phase. Carbene insertion into the adjacent C—H bond occurs, either exclusively or predominantly, with



up to 35% 1,5-C—H insertion into the alkoxy side chain to form *peri*-fused tricyclic heterocycles **236** (84AJC1915).

Heterocyclic vinylidenecarbene **237** undergoes intramolecular insertion into the C—H bond of a methoxy group, furnishing **238** (yield 84%) (82JOC5019). β -Phenoxyalkylidene carbenes, generated by the reaction alkynyl triflates **239** with phenoxide anion, undergo intramolecular aromatic C—H insertion to afford benzofurans **240** in yields of 49–62% (93TL4055).

α -Diazo- β -keto esters **241** are transformed into 3-acetylbenzofuran-2(3*H*)-ones **242** via intramolecular rhodium carbenoid insertion in greater than 90% yield (87CC1150).

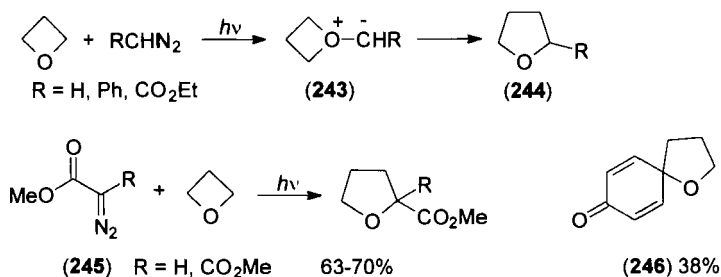
2. Oxonium Ylide Formation and Subsequent Reactions

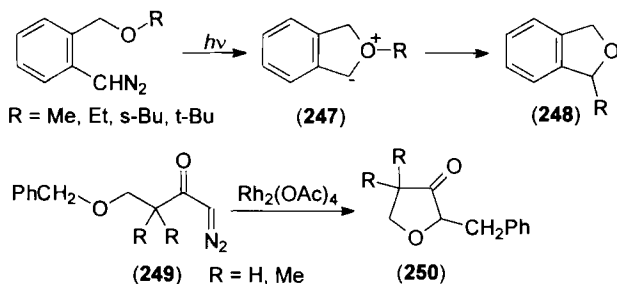
The intermolecular reaction of a carbene with an oxetane results in the formation of an oxonium ylide that is further stabilized via either opening

or expansion of the ring. Diazomethane, ethyl diazoacetate, and phenyldiazomethane were photolyzed in oxetane. In all cases, an oxolane derivative is the major (from 39 to 78%) reaction product. Carbenes more selective than methylene strongly favor electrophilic attack at oxygen over C—H insertion. The oxetane-derived ylides **243** undergo ring expansion to give oxolanes **244** in competition with intramolecular β -elimination, yielding allyl ethers (85TL193). Photolysis of diazomethane in (*S*)-2-methyloxetane gives 2- and 3-methyloxolane (1:3.2), the latter being formed with 21% net retention of configuration (85TL197). Carbenes from diazo esters **245** or aryldiazomethanes are also capable of inserting into the oxetane C—O bond (via transient *O*-ylide) to produce a five-membered O-containing heterocycle. *p*-Quinone diazide in this reaction gives spirofuran **246** (91CB1853).

Photolysis of (*o*-alkoxymethylphenyl)diazomethanes occurring via a 1,2-alkyl shift in oxonium ylide **247** leads to benzoxolanes **248** in moderate yields (42–52%) (94TL1699). Among the photolysis products of benzyloxy-methylphenyldiazomethane, a six-membered heterocycle (27%) was found, along with substituted benzoxolane (76%) (89JA1465). δ -Benzyloxy- α -diazo- β -ketones **249** in the presence of Rh(II) acetate give ylides that transform via a [1,2]-shift into 2-benzyloxolan-3-ones **250** in 64–65% yield (92JOC3479).

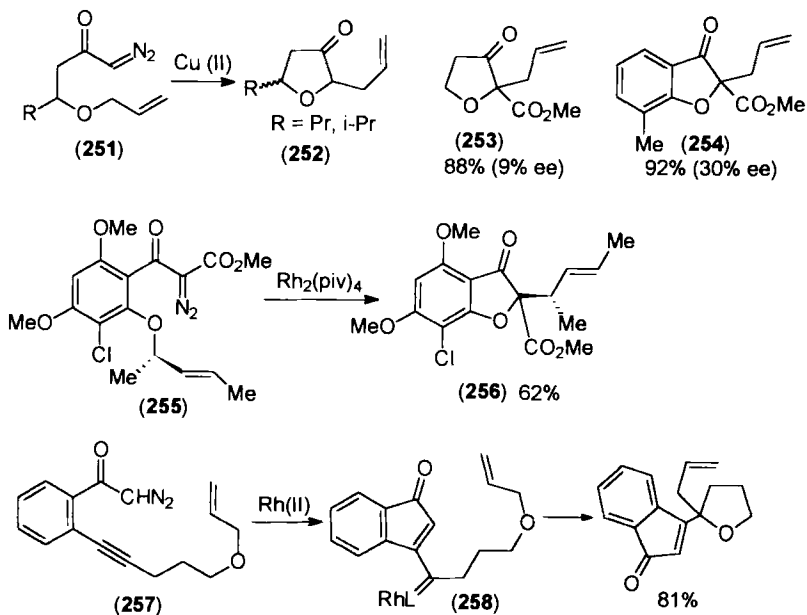
Oxonium ylides containing an allyl group on the oxygen are readily available for [2,3]-sigmatropic rearrangement. Copper(II)-catalyzed cyclization of α -diazo ketones **251** results in the formation of a mixture of *cis*- and *trans*-2,5-dialkyl tetrahydrofuran-3-ones **252**. A dramatic improvement in both the yield and degree of diastereoselectivity was achieved by employing Cu(acac)₂ as a catalyst. Optimum results were obtained when the reaction was performed in THF or benzene (*trans/cis* >97:3, 83–85%). Copper triflate also proved to be an effective catalyst for the reaction, but the yields (61–74%) and levels of diastereoselectivity (<91:7) were less satisfactory (92TL6193). Rh₂(OAc)₄-catalyzed cyclization of diazoketones and diazo-





ters proceeds with allyl migration in yields of 70–95% (86JA6060, 86JA6062). Employing a chiral rhodium–[(*S*)-(+)-BINAP] complex for decomposing methyl allyloxy-substituted α -diazo- β -ketocarboxylates results in an enantioselective [2,3]-sigmatropic rearrangement, e.g., **253** or **254** (92TL5983). The stereospecificity of the sigmatropic ylide rearrangement allows the conversion of diazo ester **255** to enantiomeric ester **256** with an asymmetric center in the alkoxy group. Ester **256** was then used in total synthesis of (+)-griseofulvin (91JA8561).

Rhodium(II) mandelate-catalyzed decomposition of diazoester **257** involves intermolecular addition of the intermediate carbenoid to the triple bond to afford the carbenoid intermediate **258**. The latter again reacts



intramolecularly with the ester oxygen, producing an oxonium ylide that further undergoes [2,3]-migration of the allyl group (92JOC4940).

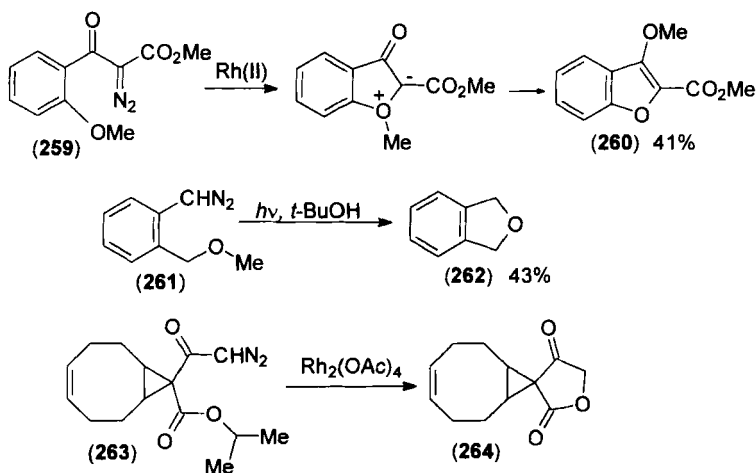
The ylide formed by an intramolecular carbene reaction with an ether oxygen atom can be stabilized either by migration of an alkyl group or by elimination of small molecules. Diazoketoester **259** gives in the presence of Rh(II) acetate an oxonium ylide that is stabilized via a [1,4]-sigmatropic migration of a methyl group to a carbonyl oxygen atom, resulting in the formation of benzofuran **260** (91JA8561).

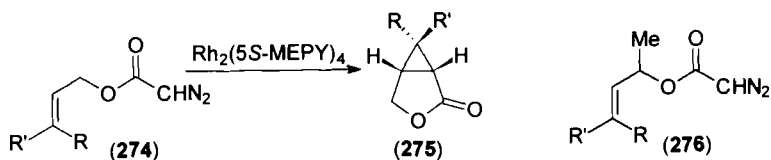
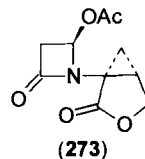
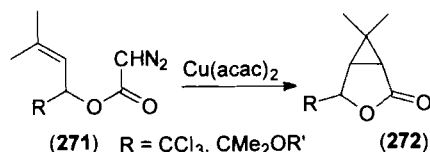
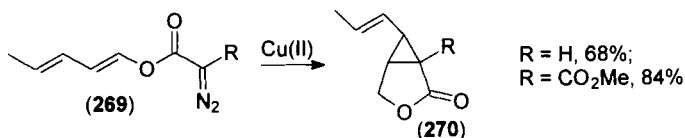
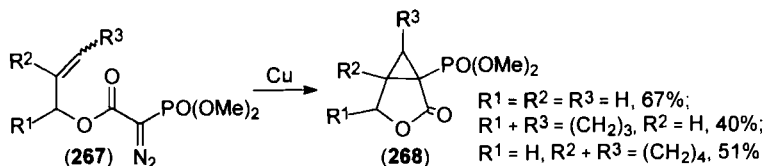
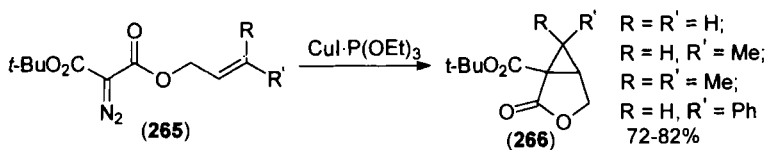
Photolysis of (*o*-methoxymethylphenyl)diazomethane **261** furnishes a carbene that is cyclized to an oxonium ylide. The latter takes up a proton and splits off a methyl cation to produce dihydrobenzofuran **262** (89JA1465).

Ketodiazooester **263** is decomposed by rhodium(II) acetate with formation of polycyclic ketolactone **264** in small yield (10%). The reaction involves the intermediate formation of an oxonium ylide stabilized by proton migration and elimination of propene (88T4363).

3. Intramolecular Cyclopropanation

Intramolecular cyclopropanation of olefinic α -diazo ketones and α -diazo esters has been widely used in organic synthesis. When a carbenoid center and the double bond are separated by a chain of three atoms, one of which is oxygen, a five-membered O-containing heterocycle is formed. Intermolecular cyclopropanations of olefins are known to allow stereospecific formation of desired products. Thus, decomposition of substituted allyl diazomalonates **265** in the presence of copper salts gives rise to bicyclic





$\text{R} = \text{R}' = \text{H}, 74\%, 88\% \text{ e.e.}; \text{R} = \text{R}' = \text{Me}, 82\%, 92\% \text{ e.e.};$
 $\text{R} = \text{Ph}, \text{R}' = \text{H}, 45\%, >94\% \text{ e.e.}; \text{R} = \text{H}, \text{R}' = \text{Ph}, 59\%, 65\% \text{ e.e.};$
 $\text{R} = \text{PhCH}_2, \text{R}' = \text{H}, 80\%, >94\% \text{ e.e.}; \text{R} = \text{Pr}, \text{R}' = \text{H}, 74\%, 75\% \text{ e.e.};$
 $\text{R} = \text{Bu}_3\text{Sn}, \text{R}' = \text{H}, 78\%, >94\% \text{ e.e.}$

γ -lactones **266**. Among the different copper(I) and -(II) salts tried for cyclopropanation, copper(I) iodide gave the highest yields (93JOC879). Asymmetric induction of cyclopropanation was observed when a chiral copper catalyst was used (93JOC4479).

β -Alkenyl phosphonacetates through α -diazo phosphonates **267** have been transformed by intramolecular cyclopropanation into γ -lactones **268**, with the best yields occurring in the presence of copper powder as catalyst (84SC155). $\text{Cu}(\text{acac})_2$ -catalyzed decomposition of diazocarbonyl **269** furnishes vinyl cyclopropane **270** in high yield (83JOC3422). A total synthesis of the synthetic pyrethroids involves stereospecific carbenoid cyclopropana-

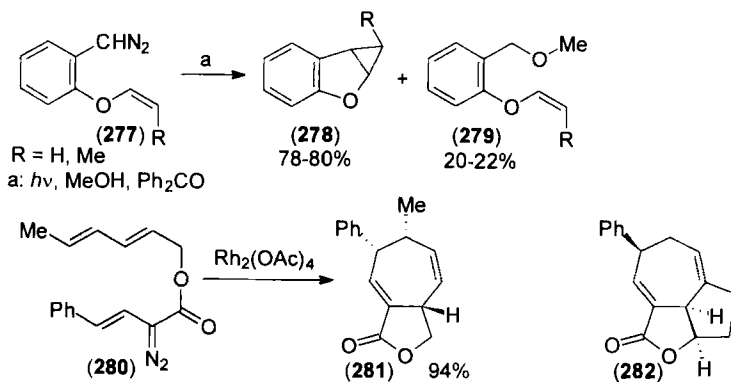
tion as the key step. Treatment of the chiral diazo esters **271** with a copper catalyst resulted in the stereospecific formation of the lactones **272** (80JOC3281; 89T7353). Lactone **273** was obtained by the same method (82JA6138).

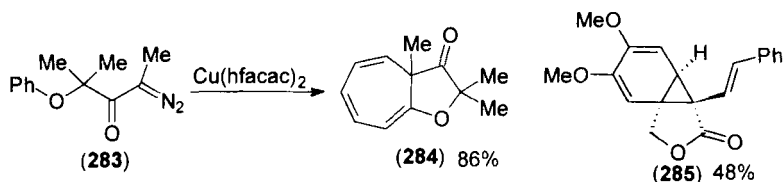
The cyclization of primary allylic diazoacetates **274** is catalyzed by the chiral rhodium complex $[\text{Rh}_2(5S\text{-MEPY})_4]$ to give cyclopropyl lactones **275** in high yield and good enantioselectivity (60 to >94%) (91JA1423; 92TL6727). The intramolecular cyclopropanation of (*Z*)-olefins is more enantioselective than the corresponding reactions of (*E*)-isomers (91JA1423). The inherent diastereoselectivity in the cyclizations of chiral secondary allylic diazoacetate **276** (R, R' as in **274**) may be effectively reversed using a chiral catalyst (94JA4493).

Photolysis of (*o*-allyloxy)phenyldiazomethanes **277** in methanol was found to give OH insertion products **278** along with cyclopropane derivative **279**. Product distributions are strongly affected by triplet sensitization in contrast to those of analogous intermolecular reactions (91JA3925).

The intramolecular reaction of the carbene from diazo ester **280**, which contains a 1,3-diene moiety in the ester group and a double bond adjacent to the carbene center, leads to the formation of a substituted 1,2-divinylcyclopropane, whose *cis* isomer then undergoes a Cope rearrangement to give substituted cycloheptadiene. In such a way, bicyclic **281** and tricyclic **282** γ -lactones with a neighboring seven-membered carbocycle have been obtained (89JOC930).

The carbene generated by copper-catalyzed decomposition of diazo-ketone **283** adds intramolecularly to the aromatic carbon-carbon bond of the phenoxy group, affording a norcaradiene derivative that then ring-opens to produce a cycloheptatriene framework fused to the γ -lactone in **284** (86T4319). Rhodium(II) octanoate-catalyzed decomposition of 3,4-





dimethoxybenzyl α -diazo ester at 0°C results in the formation of the norcaradiene **285** in 48% yield. On standing in solution at room temperature, the latter begins to undergo a Cope rearrangement to a cycloheptadiene derivative (92JOC6900).

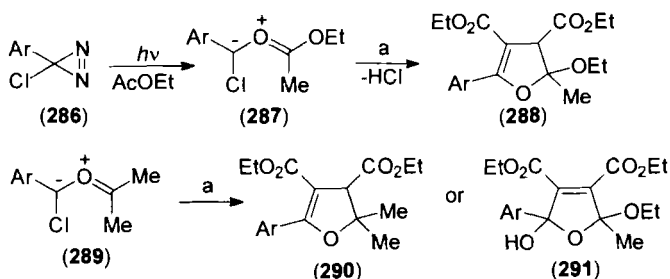
Rhodium(II) octanoate-catalyzed decomposition of diazo esters **52**, involving in the first stage a reaction of a carbenoid with the pyrrole double bond, furnishes polycyclic lactones **53** (34–79%; $\text{R} = \text{H}, \text{Me}$; $\text{R}' = \text{H}, \text{Ph}$) (94TL5209) as shown in Scheme 18.

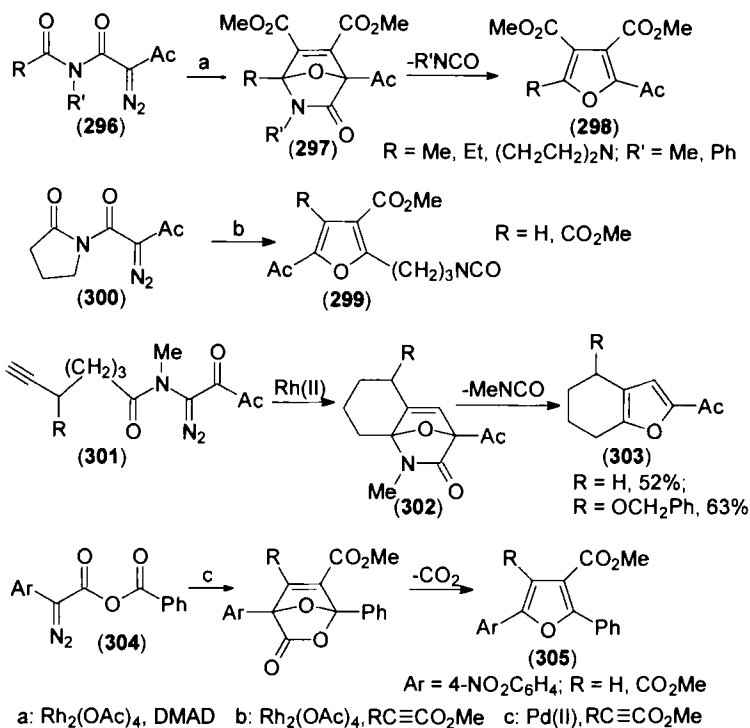
4. Carbonyl Ylide Formation Followed by [3+2]-Cycloaddition

A useful synthetic method was recently elaborated for oxolane ring creation by a [3+2]-cycloaddition reaction of a carbonyl ylide with a multiple carbon-carbon bond.

Laser flash photolysis of (*p*-nitrophenyl)chloridiazirine **286** generates the singlet arylchlorocarbene that reacts with ethyl acetate leading to carbonyl ylide **287**, which then adds to dimethyl fumarate to form dihydrofuran derivative **288** (91JA6585). Carbonyl ylide **289**, arising from the same carbene and acetone, reacts with dimethyl fumarate to yield the adduct. The latter is easily dehydrochlorinated to **290** (87TL1011) or hydrolyzed to **291** (30%) (86TL4383).

Thermal decomposition to a dihalogenocarbene from an organomercury precursor in the presence of substituted benzaldehydes and dimethyl acetylene dicarboxylate produces 2-halogeno-5-arylfuran-3,4-dicarboxylates **292** in isolated yields that range from 13 to 64%. These products appear to be the

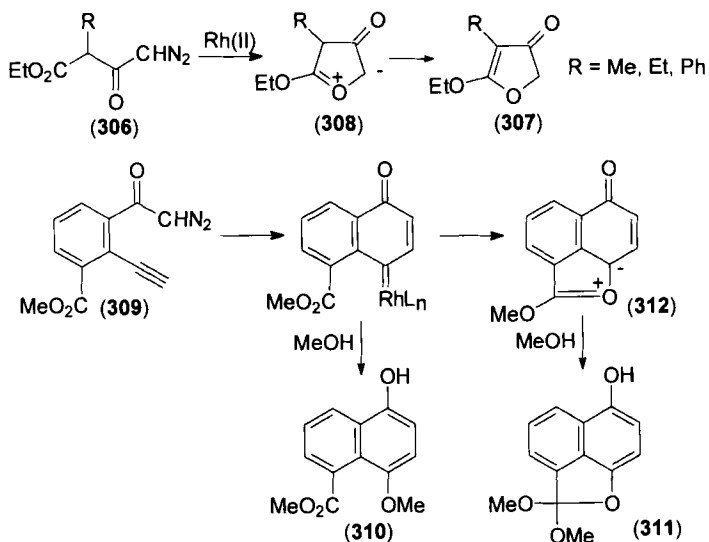




catalyzed reaction of 1-(2-diazoacetyl)-2-pyrrolidinone **300** and DMAD or methyl propiolate (69–90%) (93T2589). Analogous ketodiazooamides, containing alkynyl groups **301**, have been transformed to unstable tricyclic products **302** by a rhodium acetate-catalyzed reaction and further into bicyclic furans **303** (89CB1081).

Diazo anhydride **304** decomposes in the presence of a Pd(II) catalyst and acetylenic dipolarophiles affording, carbon dioxide and furans **305** (70–86%) (85CC190).

Cyclic carbonyl ylides may also be stabilized through H-migration or by adding nucleophilic reagents. The mechanism by which ethyl 4-diazo-2-*R*-3-oxobutylate **306** is converted into **307** (90%) involves rapid cyclization of the rhodium carbenoid onto a neighboring carbonyl group to give the cyclic carbonyl ylide **308**, which undergoes a subsequent proton transfer [91JOC3271; 92JCS(P1)2837]. The cyclization reaction of diazo ketone **309** in methanol proceeds by a similar mechanism, giving rise to a 1 : 1 mixture of **310** and **311**. The formation of **311** can be nicely accounted for in terms of the intermediacy of ylide **312**, which is trapped by MeOH (92JOC4940).

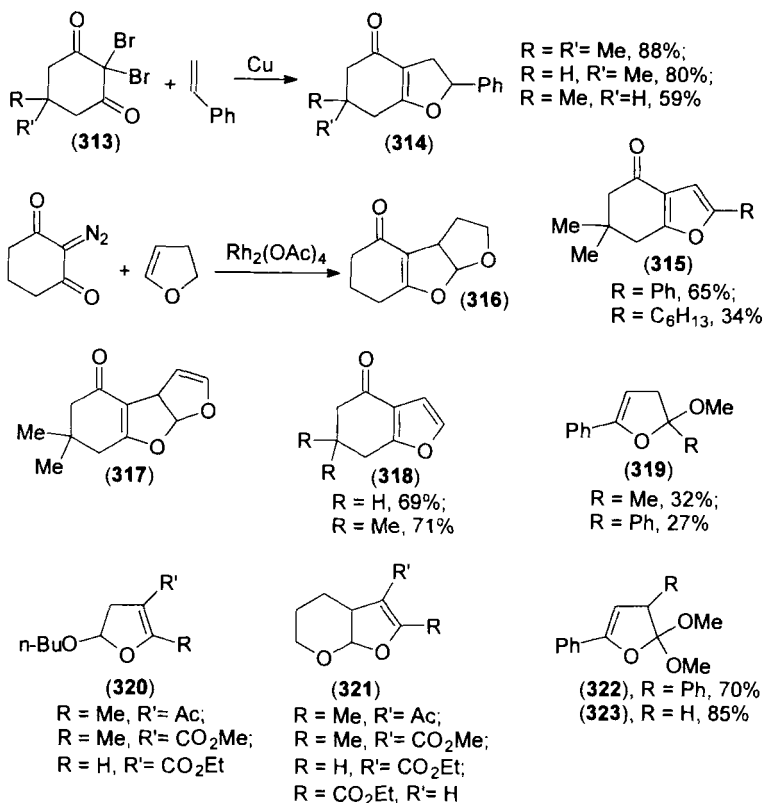


5. 1,3-Dipolar Carbene Addition and Related Reactions

Ketocarbenoid intermediates are capable of entering the 1,3-cycloaddition reaction across a double bond to furnish a 2,3-dihydrofuran ring. Substituted 2,2-dibromo-1,3-diketones **313** react with copper powder and olefins or acetylenes to give 4,5-dihydrofuran **314** or the corresponding furan **315** derivatives in a highly regioselective fashion (84TL2817; 85JOC3467).

2-Diazocyclohexan-1,3-dione reacts with 2,3-dihydrofuran in the presence of $\text{Rh}_2(\text{OAc})_4$ with the formation of heterocycle **316** in 84% yield. Analogously, adducts were obtained with furan (48%) and benzofuran (55%, two regioisomers). The reaction of diazodimedone with furan leads to product **317** (56%) (91JOC6269). The $\text{Rh}_2(\text{OAc})_4$ -catalyzed reaction of the same diazo diketones with vinyl acetate results in bicyclic furan derivatives **318**, which are formed via deacetylation of the primary products (94TL6231). This route was used in the synthesis of poganol. The chiral dirhodium–BINAP complex promotes dipolar cycloaddition of the same ketocarbene to 2,3-dihydrofuran or furan with good enantiomeric excess (44–49% e.e.) (92TL5987).

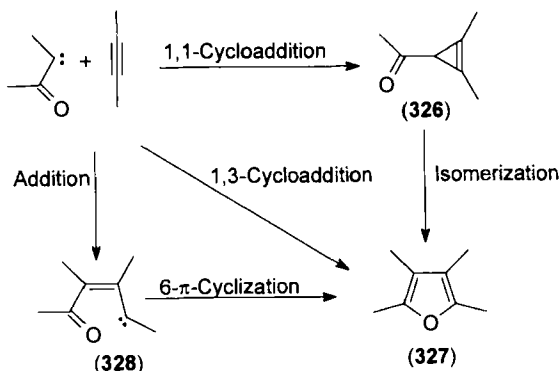
2,3-Dihydrofuran derivatives **319** are formed as major products in $\text{Rh}_2(\text{OAc})_4$ -catalyzed reactions of α -diazoacetophenone with 2-methoxypropene or α -methoxystyrene (84MI1). Copper chelate or rhodium(II) acetate-catalyzed 1,3-dipolar cycloaddition of metal carbenoids, generated from ethyl formyldiazoacetate (90JOC4975), ethyl diazopyruvate



[83JOC3047; 85JA(105)2021], methyl diazoacetoacetate, or diacetyl diazomethane (82JOC3747), with *n*-butylvinyl ether and dihydropyran gives the corresponding 2,3-dihydrofurans **320** or **321**. The $\text{Cu}(\text{acac})_2$ -catalyzed reaction between phenylketene or ketene dimethylacetal with diazoacetophenone leads to dihydrofuran **322** or **323** (85JCS(P1)289; 86JHC553).

It is extraordinary that 1,3-bis(dimethylamino)vinylcarbene **324** obtained from vinylimmonium salts, containing an acceptor group, and sodium ethoxide, adds to benzaldehyde with the formation of 2-phenyl-3-dimethylaminofuran **325** (78AG810).

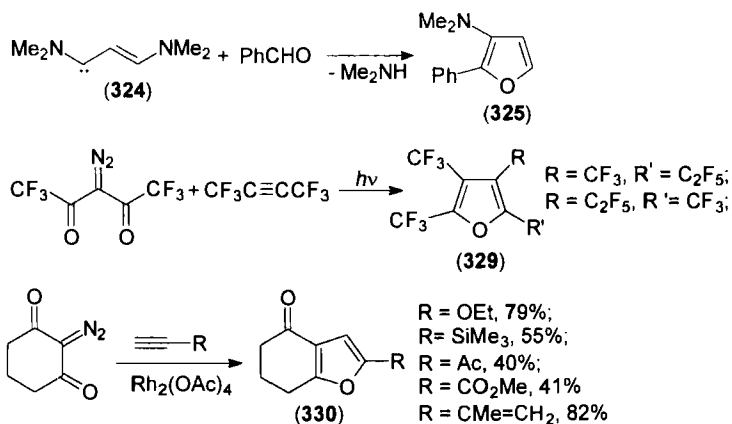
Reaction of carbonylcarbenes with a triple bond results in either 1,1-cycloaddition product **326** or 1,3-cycloaddition product **327**. Substituted furans **327** are also accessible through photolysis, thermolysis, or catalytic rearrangement of carbonylcyclopropenes **326**. However, furan formation can be imagined as a cyclization of 6π -electron system **328**, incorporating a singlet carbene or carbenoid center and a conjugated heteroatomic diene

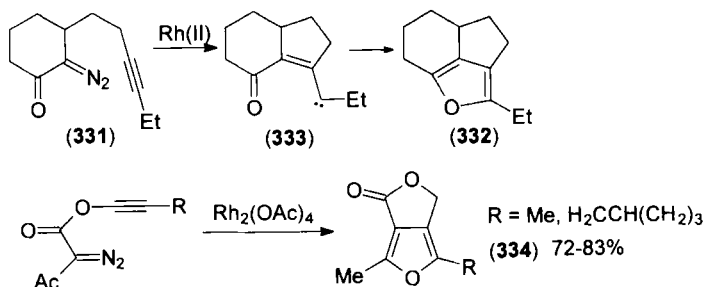


SCHEME 27

system (93JOC21), as shown in Scheme 27. Some examples of furan formation from carbenes or metal-carbenoid complexes and acetylenes are given below.

Photolysis of perfluoro-3-diazopentane-2,5-dione in perfluorobutyne leads to fluorofurans **329** (87JOC2680). The rhodium carbenoid, generated from diazo-1,3-cyclohexanedione, enters into dipolar [3+2]-cycloaddition with acetylenic compounds and forms benzofurans **330** (94TL6229). Diazo ketone **331** in the presence of a rhodium catalyst undergoes cyclization to give furan **332** in 85% yield. The reaction proceeds via formation of a transient vinyl carbene **333**, which attacks the adjacent carbonyl oxygen to give a carbonyl ylide, which subsequently tautomerizes to furan. Furan **334** was similarly obtained (90JOC414, 90TL6835; 93JOC4646). *N*-Propargyl diazomalonamic esters also give furans as shown in Scheme 24 (92JOC4404).





6. Miscellaneous Reactions

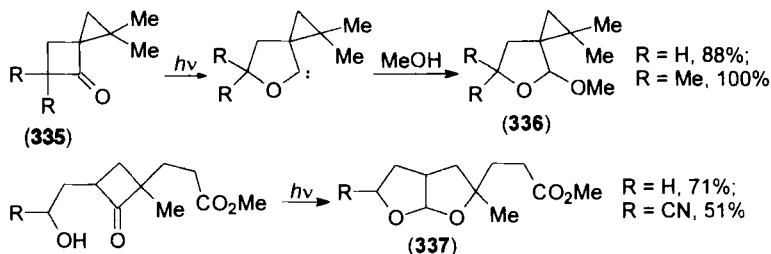
Electronically excited cyclobutanones rearrange in alcoholic media to yield products of ring expansion (2-alkoxytetrahydrofurans) (74AG200; 75ACR209). Spiro[2.3]cyclohexan-3-one **335** is, a priori, more strained than cyclobutanone and hence favors decomposition by the way of ring expansion **336** (73JA3947).

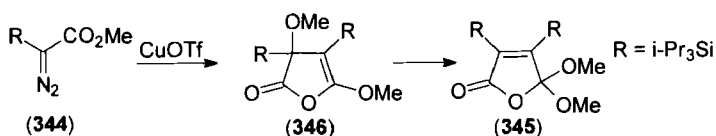
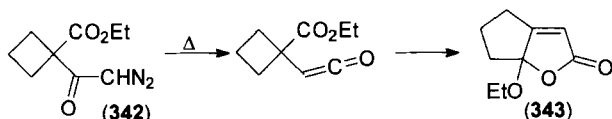
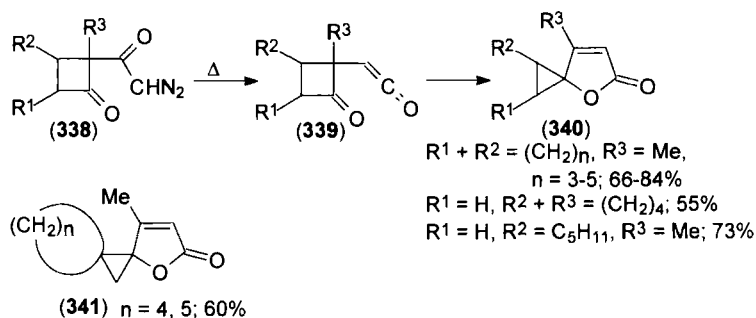
Photolysis of 2- β -hydroxyethylcyclobutanones results in a cyclic hydroxycarbene, which undergoes an intramolecular insertion into an O—H bond to afford compounds **337** (85AG1073).

Thermolysis of 2-(diazocetyl)cyclobutanones **338** furnishes 5-spirocyclopropyl- $\Delta^{\alpha,\beta}$ -butenolides via intermediate α -ketenylcyclobutanones. The method is acceptable for the synthesis of various spiropolycyclic compounds **340**, **341** in moderate to high yields (91JOC1453). Diazo compound **342** was pyrolyzed (350°C/0.1 mm) to give **343** in 40% yield (86TL2447).

Silyldiazoacetate **344** decomposes in the presence of copper triflate with the exclusive formation of the unusual carbene dimer **345** (31%). The heterocyclic framework is obtained by ketene cycloaddition to a ketocarbene dipole through intermediate **346** (92MI6).

The highly stereoselective synthesis of contiguously substituted γ -butyrolactones **347** takes place by the [2,3]-sigmatropic rearrangement of eight-

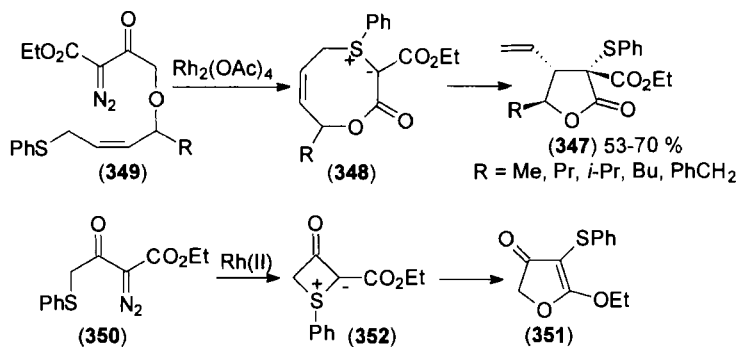




membered cyclic sulfonium ylides **348** generated by intramolecular addition from diazo sulfides **349** in the presence of rhodium(II) acetate (89TL1575; 90T4887). The $\text{Rh}_2(\text{OAc})_4$ -catalyzed decomposition of diazo ester **350** gives oxolan-3-one **351** in 50% yield. This product arises from a 1,4-rearrangement of sulfonium ylide **352** involving the ester carbonyl (87TL371).

D. SIX-MEMBERED RINGS

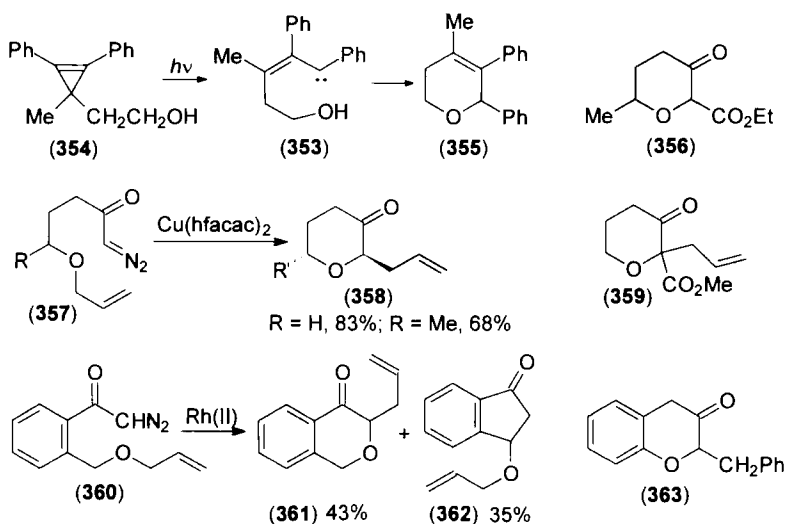
Carbene cyclization onto an oxygen atom followed by a rearrangement of the transient *O*-ylide has been widely utilized for the synthesis of pyran



derivatives. Vinyl carbene **353**, generated by photolysis of the cyclopropene derivative **354**, undergoes intramolecular O—H insertion, producing dihydropyran ring **355** (80JOC2181). On treatment with rhodium(II) acetate in benzene, ethyl 2-diazo-6-hydroxy-3-oxoheptanoate cyclizes to the corresponding cyclic ether **356** in 80% yield (87TL5351).

Decomposition of diazo compounds **357** in the presence of $\text{Cu}(\text{hfacac})_2$ proceeds via a cyclic oxonium ylide, which is stabilized by a [2,3]-sigmatropic shift of the allyl group to give cyclic ethers **358** (93TL4385). Ether **358** ($\text{R} = \text{Me}$) was used in the synthesis of decarestridine L (94TL6381). Similarly, ester **359** was obtained from the corresponding keto diazoester in 53% yield (86JA6060). Rhodium(II) acetate proved to be less advantageous as a catalyst because appreciable amounts of C—H insertion products were formed.

Oxonium ylides generated by cyclization of *O*-allyloxy- or *O*-benzyloxy-arylcarbenes onto the ether oxygen atom are known to undergo [2,3]- or [1,2]-sigmatropic rearrangements, as well. Padwa and co-workers have shown that the rhodium(II) acetate-catalyzed reaction of diazo ketone **360** leads to a mixture of two compounds. The formation of major product **361** is consistent with carbenoid generation followed by trapping of the latter by the neighboring oxygen atom to produce an oxonium ylide that further undergoes a [2,3]-sigmatropic shift. The minor product **362** is a result of a carbenoid C—H insertion reaction (89JOC817). 3-(*o*-Benzyloxyphenyl)-1-diazoacetone in the presence $\text{Rh}(\text{II})$ catalyst yields 67% of cyclic ether **363** via [1,2]-benzyl migration in the intermediate oxonium ylide (92JOC3479).



The $\text{Rh}_2(\text{pfb})_4$ -catalyzed conversion of 1-diazo-2,5-dicarbonyl compounds **364** occurs via cyclic carbonyl ylides **365** stabilized by 1,4-H-migration to produce dihydropyrans **366** in 60–85% yield (92JCS(P1)2837).

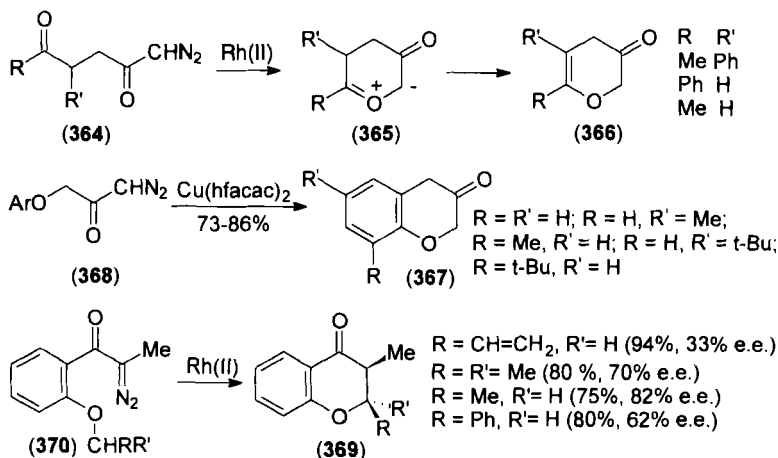
Intermolecular insertion into the C—H bonds and addition to the C=C bonds provide a convenient route to a variety of pyran derivatives.

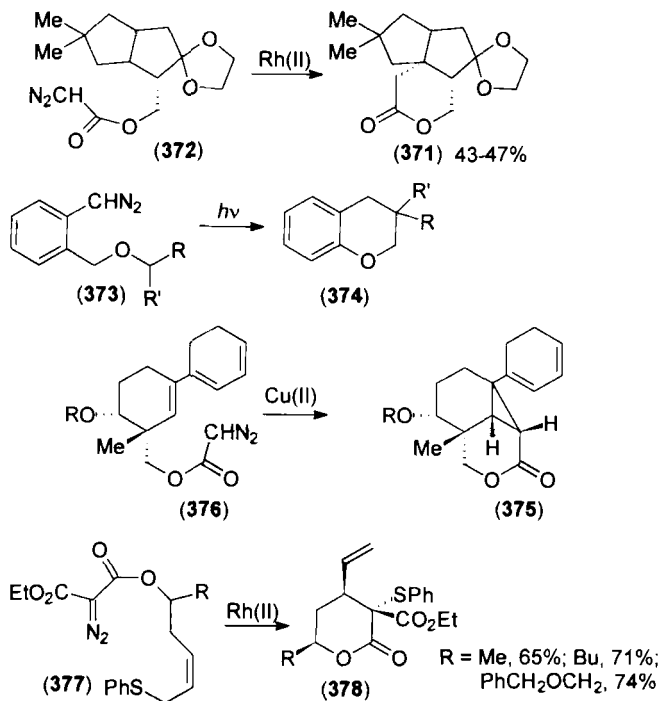
The synthesis of the 3-oxo-3,4-dihydro-2*H*-1-benzpyran ring system **367** in high yields was effected by the decomposition of 1-diazo-3-aryloxy-2-propanones **368** in the presence of catalytic amounts of $\text{Cu}(\text{hfacac})_2$ (84S268; 86T4319). This reaction proceeds as a very selective intermolecular carbene C—H insertion.

The synthesis of substituted chromanones **369** via a C—H insertion reaction of α -diazo ketones **370** has demonstrated that high levels of enantioselectivity are attainable through the use of chiral rhodium carboxylates (92CC823). Treating diazo ketone **370** ($\text{R} = \text{CH}=\text{CH}_2$, $\text{R}' = \text{H}$) with $\text{Rh}_2[(S)(+)\text{BINAP}]_4$ leads enantioselectively to the *cis* isomer of chromanone **369** (92TL5983).

Tricyclic compound **371** was produced from diazoacetic ester **372** by the rhodium(II) acetate-catalyzed insertion into the C—H bond at the tertiary C atom and located in the ϵ -position with respect to the diazo group (84JA5295). [2-(Alkoxyethyl)phenyl] carbenes generated by the photolysis of diazo compounds **373** undergo intramolecular C—H insertion with the formation of benzodihydropyran derivatives **374** in 32–96% yield (89JA1465; 94TL1699).

The enantioselective total synthesis of antheridic acid involves the key *O*-heterocyclic intermediate **375** produced by an intramolecular addition





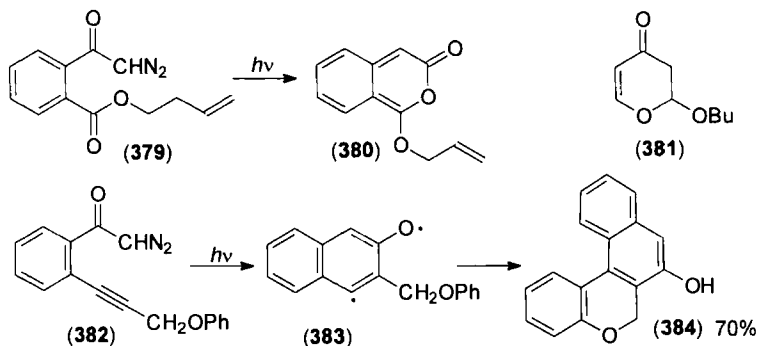
of a copper-carbenoid to the carbon-carbon double bond of compound **376** in 76% yield [84TL3559; 85JA(107)5574; 91TL5025]. Homoallylic ester of diazomalonic acid in the presence of $\text{Cu}(\text{acac})_2$ forms the corresponding bicyclic δ -lactone in 35% yield (81JOC5255).

The rhodium(II) acetate-catalyzed decomposition of diazomalones **377** via a [2,3]-sigmatropic rearrangement of an intermediate *S*-ylide affords mixtures of stereoisomeric vinyl-substituted valerolactones **378** with prevalence of *cis* isomers (90CC418, 90T4887).

Photolysis of diazo ketone **379** generates an arylketene by a Wolff rearrangement following the intramolecular [4+2]-cycloaddition with a $\text{C}=\text{O}$ bond; this leads to benzopyrone **380** in 78% yield [92JCS(P1)2837].

2-Butoxy-2,3-dihydropyran-4-one **381** was prepared in 70% yield by refluxing diazomalonaldehyde in butylvinyl ether. Presumably, the loss of nitrogen from the diazo compound was accompanied by a hydrogen 1,2-shift yielding formylketone, whose [4+2]-cycloaddition with enol ether liberated the six-membered heterocycle (90JOC4975).

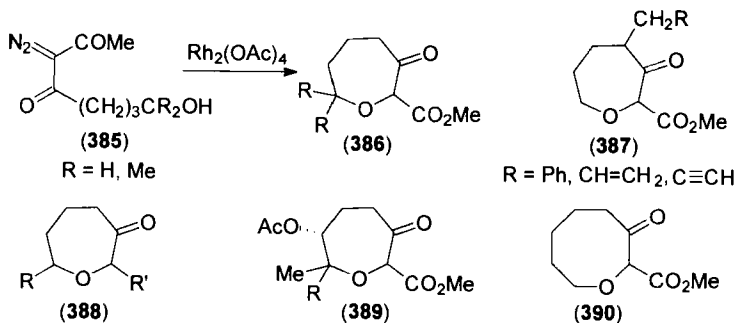
Irradiation of aryl diazo ketone **382** produces arylketene, which undergoes intramolecular cycloaromatization onto an *o*-alkynyl substituent with



the formation of diradical intermediate **383**. The latter undergoes further cyclization with a phenoxy group to give naphthol **384** (93JOC6429).

E. SEVEN-MEMBERED AND LARGER RINGS

Treatment of diazo esters **385** with a catalytic amount of rhodium(II) acetate resulted in their rhodium carbenoid-mediated cyclization to oxepanes **386** in 72–78% yield [86TL1403; 88JCS(P1)1417]. Oxepane derivatives **387** were prepared in useful yields from diazo alcohols with rhodium(II) acetate, acetamide, or perfluorobutyrate catalysts (93T5109). This methodology was also utilized in the synthesis of 2,7-disubstituted oxepanes **388** ($R = H, Me, C_6H_{11}$; $R' = CO_2Et$) [87TL5351; 89JCS(P1)721]. Cyclization of diazo alcohols resulting in functionalized oxepanes **388** [48–64%; $R = H, C_6H_{13}$; $R' = CO_2Bu-t, Ac, Me_3Si, SO_2Ph, PO(OEt)_2$] is the key step in synthesis of isolaurepinnacine [91JCS(P1)1]. A synthetic approach to the oxepane diterpene zoapatanol includes the formation of cyclic ether



389 [$R = i\text{-BuCH}_2\text{CH}_2, (\text{CH}_2\text{O})_2\text{CHCHMe}(\text{CH}_2)_3$] by rhodium carbenoid cyclization [89JCS(P1)2473].

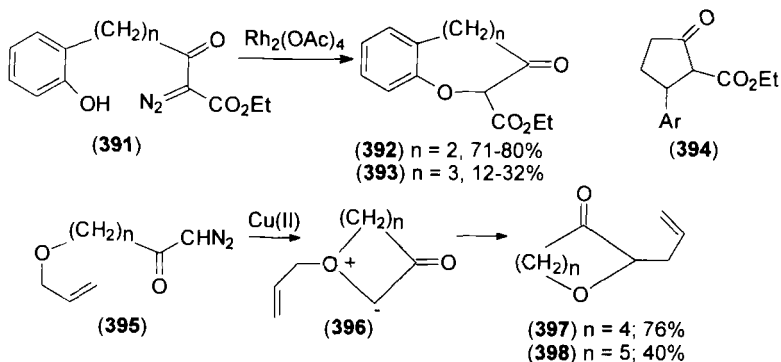
3-Oxooxocane derivative **390** was produced by this method in 24% yield. However, such an approach proved to be unsuccessful for producing ten-membered cyclic ethers [86TL1403; 88JCS(P1)1417].

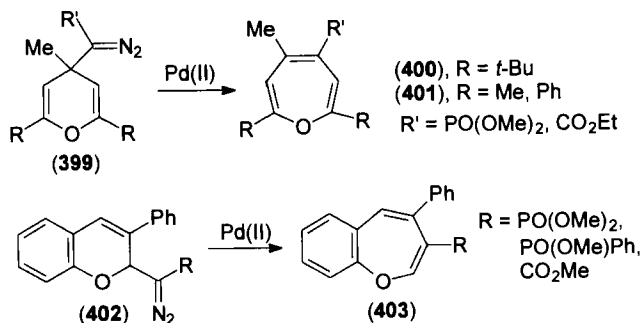
Diazo compounds **391** containing *o*-hydroxyphenyl groups give benzo-oxepane **392** or benzoxocane **393**. Similarly, a seven-membered benzo-fused ether **392** has been obtained in a yield greater than that of the eight-membered ether **393** [86TL1403; 87TL5351; 88JCS(P1)1417; 89JCS(P1)721]. While the yield of ether **393** was low, the major product was cyclopentanone **394**, formed through a competing C—H insertion at the benzylic position.

Decomposition of 6- or 7-allyloxy α -diazocarbonyl compounds **395** in the presence of a copper(II) catalyst produces copper carbenoids, which undergo intramolecular addition onto an ether oxygen to give oxonium ylide **396**. The latter rearranges through a [2,3]-sigmatropic allyl migration furnishing 2-substituted cyclic ethers **397** or **398** in high yields. Copper(II) hexafluoroacetylacetonate serves as an extremely efficient catalyst, thereby reducing the contribution of the competitive C—H insertion to a minimum (93TL4385).

Decomposition of 4-diazomethyl-4*H*-pyrans **399** in the presence of a Pd(II) catalyst provides near quantitative yields of oxepins **400** (85CB3700) and **401** (87JOC3851). Analogously, in the μ -allylpalladium chloride-catalyzed decomposition of 2-diazomethyl-2*H*-1-benzopyrans **402**, benzo-xepines **403** are formed via ring expansion in 50–78% yield (87CB1397).

Oxepin **404** was prepared by the reaction of ethyl diazopyruvate with 1,3-butadiene in 26% yield. The reaction involves a carbene addition to the double bond with formation of a mixture of *cis*- and *trans*-2-oxo-2-(2-

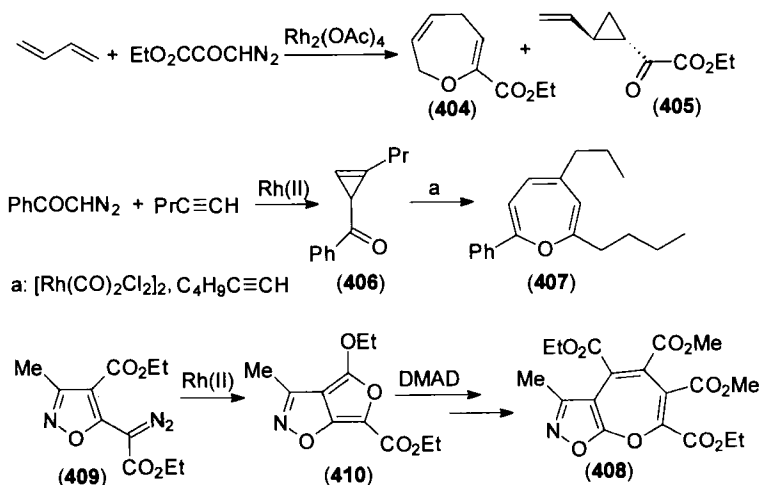




vinylcyclopropyl)acetates. The *cis* isomer is unstable and turns into the product through a Cope rearrangement (87HCA2159). The *trans* isomer **405** (yield 35%) can easily be transformed into *cis*-**405** on photolysis.

Benzoyldiazomethane reacts with a terminal alkyne in the presence of a rhodium catalyst to give cyclopropene **406**. The resulting cyclopropene was allowed to react with another terminal alkyne in the presence of tetracarbonyldichlorodirhodium, affording oxepin **407** (92JA5881).

The oxepino[2,3-*d*]isoxazol system **408** was prepared in 77% yield from diazo ester **409** and DMAD with a rhodium(II) acetate catalyst. The transient furoisoxazole **410** undergoes 1,5-electrocyclization to a carbene, which yields the final products via reaction with DMAD followed by a series of consecutive transformations (91TL1161).



V. Synthesis of Rings with One Sulfur Atom

A. THREE-MEMBERED RINGS

The formal addition of a carbene to a C=S bond provides one possible route to the thiirane ring. An example is found in the synthesis of methylene-thiirane **411** by reaction of di-*tert*-butylthioketene with dimethyl diazomalonate in the presence of $\text{Rh}_2(\text{OAc})_4$ (89TL1249). The interaction proceeds via an unstable thioketene *S*-methylide **412**, which undergoes 1,5-cyclization to the corresponding oxathiole at 50°C (Section VII,B,4), and at higher temperatures undergoes 1,3-cyclization to thiirane **411** (66%).

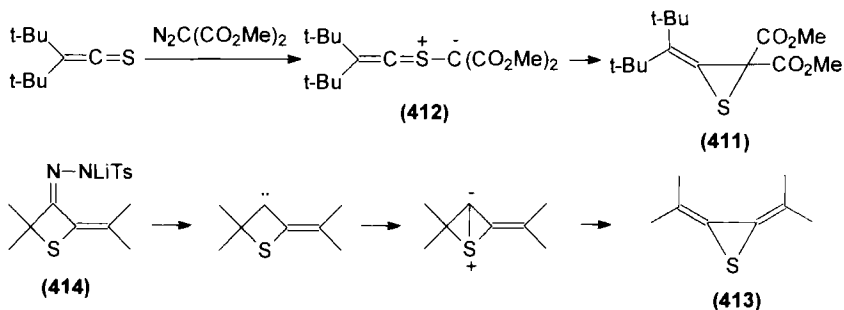
The thietane ring contraction with bicyclic ylide intermediacy is the basis of the synthesis of "thiiradialene" **413** by vacuum pyrolysis of tosylhydrazzone lithium salt **414** (81TL4815).

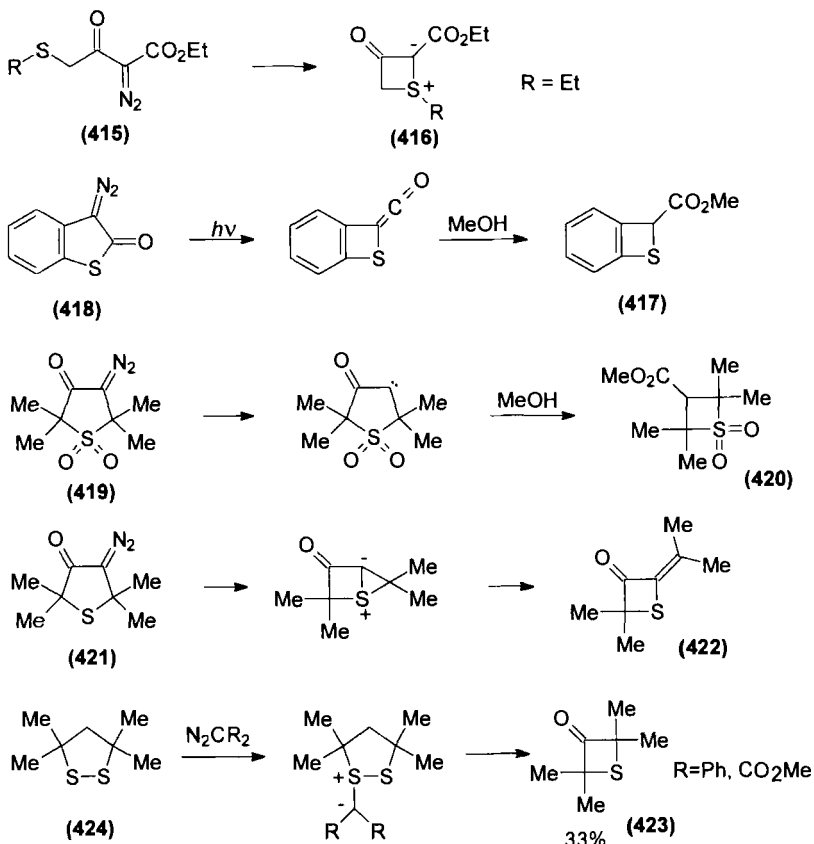
B. FOUR-MEMBERED RINGS

Cyclization of diazo sulfides **415** offers a route to stable four-membered cyclic ylides; thus, for example, compound **416** (R = Et) was isolated in 53% yield. However, attempts to cyclize sulfide with a phenyl substituent have been unsuccessful (87TL371).

Ring-contraction-based methods for producing thietanes involve a Wolff rearrangement and the rearrangement of thiolanylidenes via bicyclic sulfonium ylides. The formation of benzothietane **417** occurs through a Wolff rearrangement of the intermediate carbene, derived from diazo ketone **418** (77CB2242). Thermolysis of sulfone **419** again involves a Wolff rearrangement of the intermediate carbene to an unstable ketene, giving rise to **420** upon solvolysis.

In five-membered cyclic diazo ketones containing a bivalent sulfur atom, intramolecular ylide formation with subsequent ring contraction becomes





possible. Such a reaction sequence is operative in the decomposition of ketone **421** in refluxing isooctane, furnishing thietanone **422** quantitatively (80JOC4804; 82JOC4429).

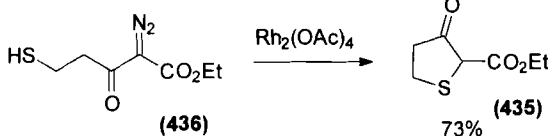
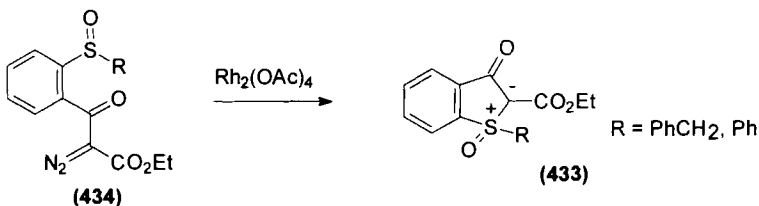
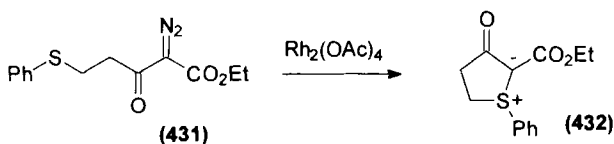
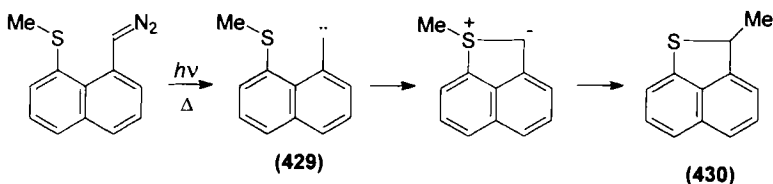
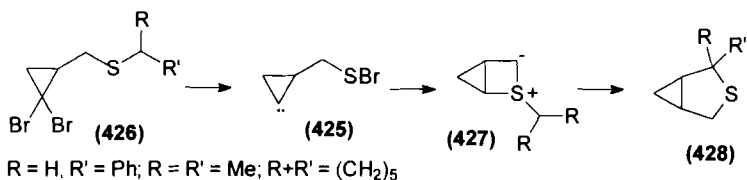
Thietanone **423** is obtained by desulfurization of cyclic disulfide **424** under the action of bis(methoxycarbonyl)carbene or dkphenylcarbene, generated from the corresponding diazo compounds (85TL5187). This transformation takes place only with disulfides containing bulky substituents. Otherwise, carbene insertion into the S—S bond proceeds with ring expansion (Section VII,C,1).

C. FIVE-MEMBERED RINGS

Carbene cyclization reactions offer a convenient and efficient method for the synthesis of five-membered sulfur-containing rings. These may involve both carbene insertion into a C—H bond and ylide formation.

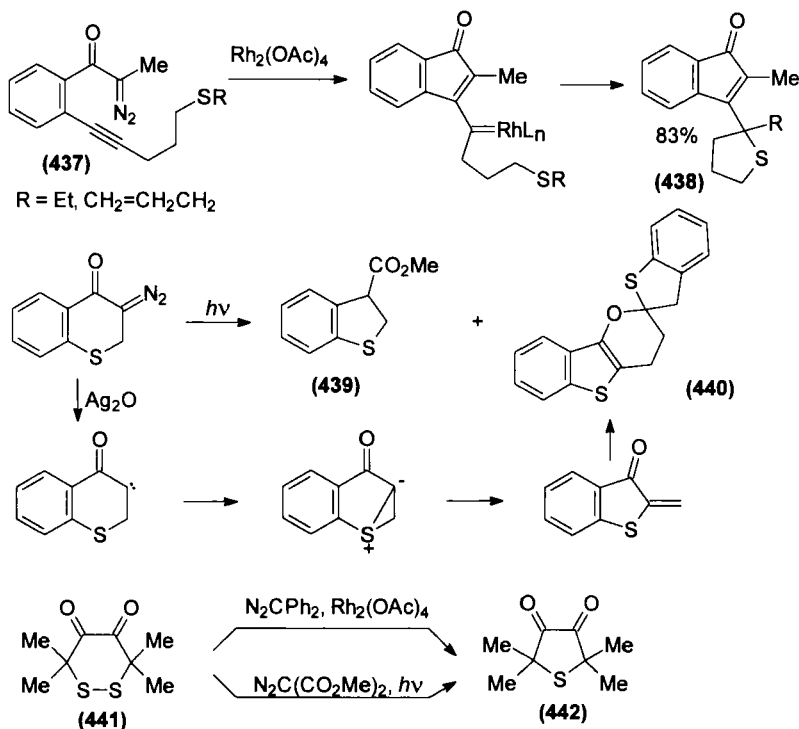
The formation of free carbene **425** was postulated in the reaction of sulfides **426** with methylolithium. It is stabilized via cyclization into a four-membered sulfonium ylide **427**, followed by rearrangement with ring expansion into thiabicyclo[3.1.0]hexane **428**, which is isolated as a mixture of *endo* (72%) and *exo* (28%) isomers in an overall yield of 17–38%. However, simultaneous occurrence of side processes makes this reaction synthetically inappropriate [82ACS(B)593].

Free carbene **429** generated by photolysis or thermolysis of the diazo compound cyclizes into the sulfonium ylide, which undergoes a thia-Stevens rearrangement to **430** in 19% yield. The same result was obtained using the corresponding *p*-tosylhydrazone sodium salt as a carbene precursor (83JA6096). Rh(II)-catalyzed decomposition of sulfur-containing diazo (83JA6096). Rh(II)-catalyzed decomposition of sulfur-containing diazo



compounds generally occurs unidirectionally and provides higher product yields. Reactions of diazodicarbonyl compounds result, as a rule, in stable sulfur ylides. Thus, $\text{Rh}_2(\text{OAc})_4$ -induced decomposition of diazo sulfide **431** affords ylide **432** in 69% yield (87TL371). Moody *et al.* (88TL6009) have demonstrated that stable five-membered cyclic imides can be produced from diazo sulfoxides. Ylides **433** were obtained in 58 and 78% yields from the decomposition of diazo compounds **434**. When a phenylthio group in a diazocarbonyl compound of type **431** is replaced by SH, a product of formal S—H insertion is formed. An example is found in the preparation of thiophene **435** from diazo thiole **436** (85JOC5223).

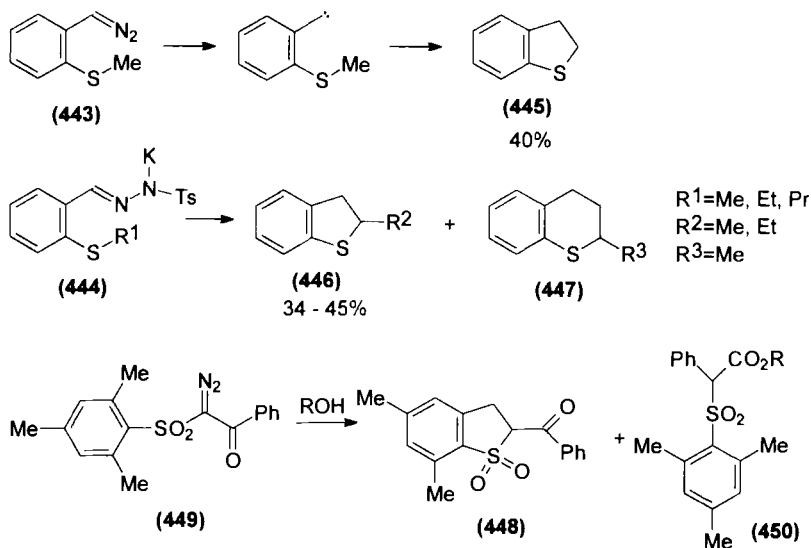
Recently, the known method for the synthesis of thiolanes by cyclization of diazo ketosulfides (72CC860) has received further development (92TL169; 95JOC53). It was found that sulfur-containing α -diaz ketones **437** bearing a tethered alkyne unit decomposed in the presence of $\text{Rh}_2(\text{OAc})_4$ via the addition of the rhodium-stabilized carbenoid onto the acetylene π -bond to give a vinyl carbenoid, followed by sulfonium ylide formation and a subsequent [2,3]- or [1,2]-sigmatropic shift. This transfor-



mation with carbene center displacement occurs with both alkylthio- and allylthio-substituted diazo ketones and furnishes high yields of thiolanes **438** (95JOC53).

The six-membered ring contraction-based methods for the synthesis of thiolane derivatives are analogous to those mentioned above for thietanes (Section V,B). Wolff-like rearrangement of 3-diazothiochroman-4-one gives ester **439** (24%) with impurity of **440** (8%) (80CPB3430). The formation of the latter was rationalized in terms of a competing carbene cyclization with subsequent thiirane ring opening in the bicyclic sulfide. Notably, in boiling methanol in the presence of Ag_2O this reaction affords exclusively **440** in 44% yield. Bulky disulfide **441** undergoes desulfurization under the action of diphenylcarbene generated by catalytic decomposition of diphenyldiazomethane or bis(methoxycarbonyl)carbene by photolysis of dimethyl diazomalonate to give thiolane **442** (85TL5187).

Carbene insertion into an aliphatic C—H bond is impractical in S-containing heterocycle synthesis because of its poor regioselectivity. Thus, on heating diazo compound **443** (83JA6096) in chlorobenzene, or *p*-tosylhydrazone potassium salt **444** in the gas phase (79AJC99), **445** and **446** were obtained along with products of dimerization of the intermediate carbenes, products of interactions of the latter with the initial diazo compounds, and products of carbene insertion into the C_β —H bonds of **447**. Benzo[*b*]thiophene 1,1-dioxide **448**, resulting from carbene insertion, was obtained as a by-product (12–21%) during the decomposition of diazo

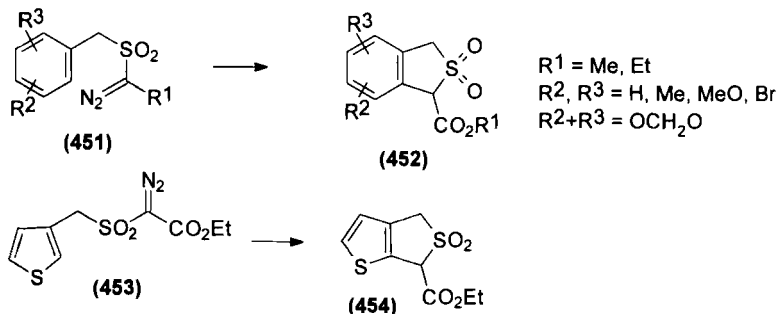


sulfone **449** in refluxing toluene in the presence of alcohols. The main route of stabilization of the intermediate benzoylsulfonylcarbene here was a Wolff rearrangement with formation of the corresponding ester **450** (82CPB899).

Carbene insertion into an aromatic C—H bond provides a route to 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxides, valuable precursors of *o*-quinodimethanes used in steroid synthesis (86TL5679). The intramolecular insertion of Rh(II) carbenoids, generated from diazo compounds **451**, into a C—H bond occurs at room temperature to give target compounds **452** in 14–48% yield. Notably, the reaction has a propensity to give products arising from attack at the carbon *para* to the existing electron-donor substituent in cases where a competition between *ortho* and *para* is possible. No isomeric by-products were detectable, showing the high regioselectivity of the process. This reaction does, however, have some limitations from the preparative point of view. Thus, attempts to annelate a thiophene ring to an *ortho*-methoxy-substituted benzene ring have failed. Furthermore, by contrast to the α -diazo ester **451**, α -diazo ketones and sulfonyl diazo-methanes give only intractable tars under the same conditions. Nevertheless, the carbene insertion reaction can be of preparative value with thiophene derivatives. Thus Rh(II)-catalyzed decomposition of diazo compound **453** furnishes thiopheno[2,3-*c*]thiophene **454** in 49% yield (86TL5679).

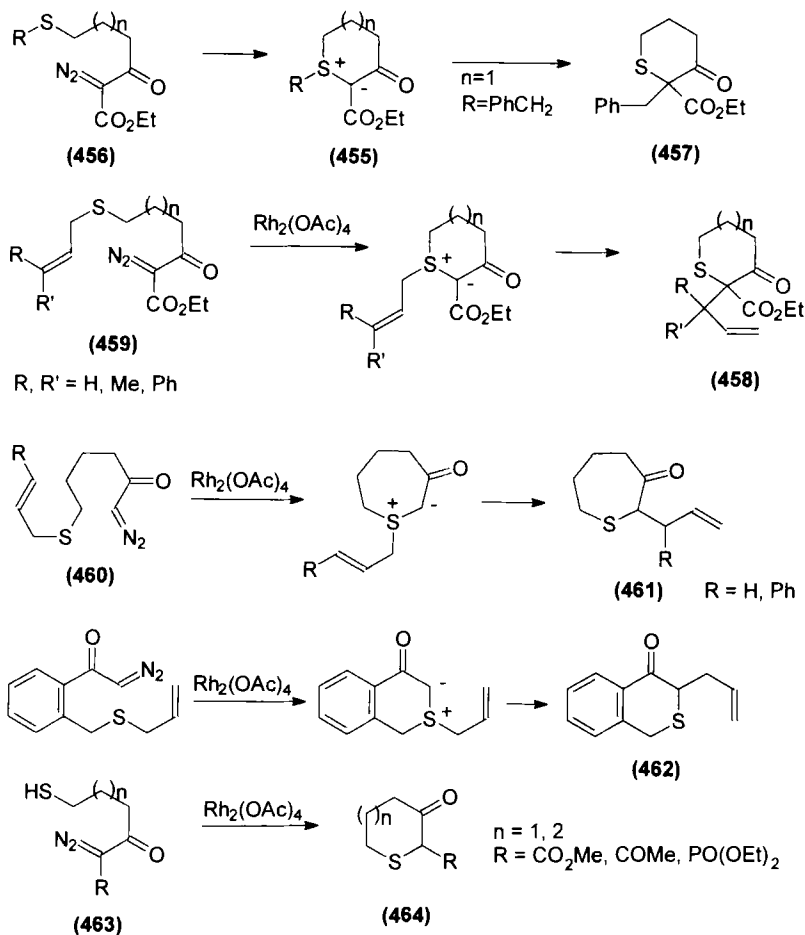
D. SIX- AND SEVEN-MEMBERED RINGS

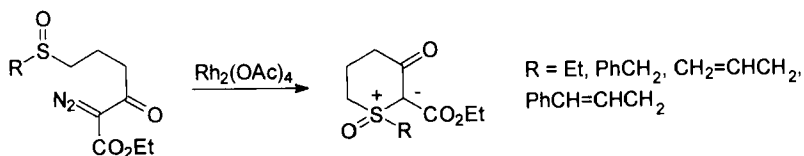
The most important methods for the synthesis of thiane and thiepane derivatives involve sulfonium ylide formation. The most graceful and effective of these is the intramolecular cyclization of carbenes derived from diazocarbonyl and diazodicarbonyl compounds. In some cases, the latter provide stable sulfonium ylides. Thus, ylides **455** ($n = 1$; R = Et, Ph) were produced on heating diazo compounds **456** ($n = 1$; R = Et, Ph) in 62 and



7% yield, respectively (87TL371; 88TL6005). Decomposition of **456** ($n = 1$; $R = \text{PhCH}_2$) provides the corresponding **455** in poor yield (24%); this is presumably due to the high migratory ability of the benzyl group, which reveals itself in the transformation of **455** ($n = 1$; $R = \text{PhCH}_2$) to **457** in refluxing xylene. The moderate yield of thiapane **455** ($n = 2$; $R = \text{Ph}$) is explainable in terms of a competitive aliphatic C—H insertion. Since the intermediate *S*-allyl sulfonium ylides are readily available for symmetry-allowed [2,3]-sigmatropic rearrangement, only thianes **458** could be isolated upon decomposition of **459** (59–78%). The thiapane derivative **458** ($n = 2$; $R^1 = \text{H}$, $R^2 = \text{Ph}$) was, however, obtained in just 26% yield (90T6501).

Diazocarbonyl precursors of Rh(II) carbenoids proved to be of particular efficiency in the synthesis of seven-membered rings. Thus, thermocatalytic





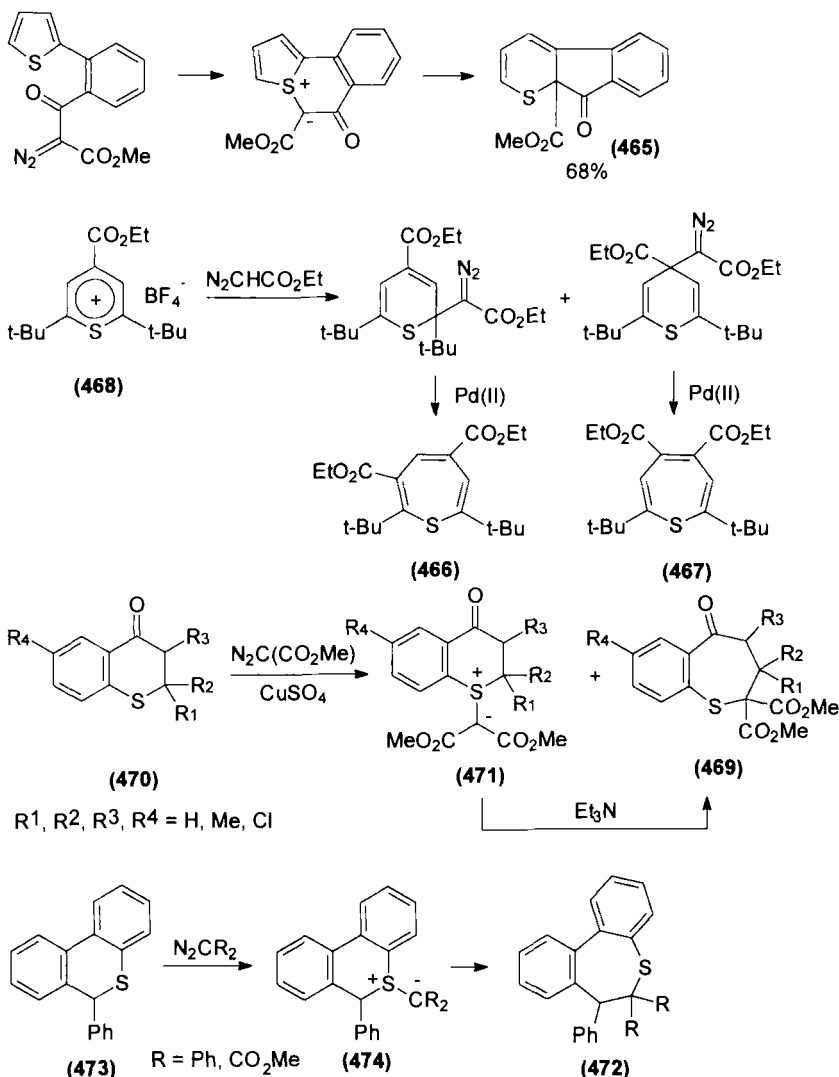
SCHEME 28

decomposition of diazo sulfides **460** furnishes good yields of thiepanes **461** (42–64%) (88TL6005; 90T6501). The yield of fused thiane **462** is 89% (76LA641; 89JOC817). The satisfactory results with thianes and thiepanes suggest diazo thioles as carbenoid precursors. Decomposition of **463** proceeds through cyclic ylide formation followed by a [1,2]-H-shift to afford compounds **464** in 34–80% yield (85JOC5223; 87TL5351; 90T6501).

The intramolecular cyclization of Rh(II) carbenoids onto a sulfoxide S atom allows one to obtain stable sulfoxonium six-membered cyclic ylides. Interestingly, even with allylic-type substituents at the S atom, this reaction stops at the stage of ylide formation, the yields attaining 84% (Scheme 28) (88TL6009).

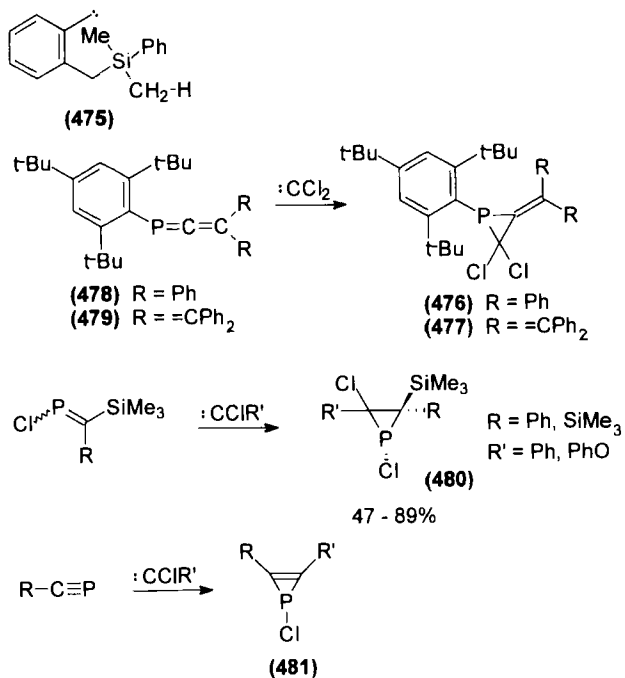
Cyclization of a carbenoid onto the S atom incorporated into a heterocycle is accompanied by structural rearrangement with ring-size variation. Thus, **465** was obtained as the result of thiophene ring expansion through the sequence of cyclization with ylide formation and Stevens rearrangement (84CC208). The attempted synthesis of type-**465** thiepine containing no ester group from a corresponding diazo ketone was unsuccessful. However, the diazo ketone methylated at the C₃- and C₅-position of the thiophene ring is partially transformed to unstable thiopyran **465**, which can be detected spectroscopically [86ACS(B)303]. Isomeric thiepinines **466** and **467** were readily prepared by a two-step procedure, starting from thiapyrylium salt **468** and ethyl diazoacetate and going through a stage of thiine ring expansion for an overall yield of 75% (85CL1119).

The intermolecular version of cyclic sulfur ylide formation from carbenes has been explored by Tamura *et al.* in a convenient route to benzo[*b*]thiepanes **469** [81JCS(P1)2978]. The reaction of thiochroman-4-ones **470** with dimethyl diazomalonate usually gives a mixture of ylide **471** and benzothiepane **469**. But when this mixture was treated with Et₃N, compounds **469** were obtained with good yields. In the analogous synthesis of **472** (R = CO₂Me) from thiane **473** (R = CO₂Me), the ring expansion in ylide **474** required heating up to 175°C, whereas seven-membered ring formation in a reaction with diphenylcarbene occurs even on refluxing in benzene. With substrates unsubstituted in the C₁-position, the reaction produces no similar products [82JCS(P1)917].



VI. Synthesis of Rings with One Other Heteroatom

Carbene reactions are of virtually no synthetic importance for silicon-containing heterocycles, mostly because of the poor selectivity of the carbene insertion processes involved. Thus cyclization of carbene **475** may be effected via C_{alkyl}—Si, C_{aryl}—Si and C—H bond insertions as well as via



cyclopropanation of the benzene ring with cycloheptatriene formation. Five-, six-, seven-, and eight-membered silicon-containing heterocycles can be formed simultaneously [90AG(E)661; 94JOC3821]. Singlet methylene ($^1\text{CH}_2$), produced by the photolysis of ketene, demonstrates similar behavior in a reaction with silacyclobutane (89CC284).

Phosphiranes and phosphirenes are the only phosphorus-containing heterocycles available so far via carbene reactions. Without exception, these reactions involve 1,2-cycloaddition of a carbene to $\text{C}=\text{P}$ or $\text{C}\equiv\text{P}$ multiple bonds. Using the 2,4,6-tri-*tert*-butylphenyl moiety as a sterically protective group, Yoshifuji and co-workers have successfully synthesized methylenephosphirane **476** (91CC124) and vinylidenephosphirane **477** (91TL6879) by treating the corresponding phosphoallene **478** and phosphina-1,2,3-butatriene **479** with dichlorocarbene. Preparatively useful yields of phosphiranes **480** are obtained in reactions of diazirine-derived chlorocarbenes with P-chloro-substituted phosphoalkenes that proceed with complete diastereoselectivity (89TL3951). The addition of chlorocarbenes generated from diazirines to the $\text{C}\equiv\text{P}$ bond of phosphoalkenes occurs as easily. However, the 2*H*-phosphirene primary products could not be isolated since they undergo isomerization to 1*H*-phosphirenes **481** by a rapid [1,3]-chlorine shift [89AG(E)225].

By Cu-catalyzed decomposition of *ortho*-seleno- and -telluro-substituted ω -diazoacetophenones, Lohner and Praefcke **482** synthesized seleno- and telluro-3-coumaranones **483**. This reaction with the participation of a free carbene generated by photolysis of **482** ($Z = \text{Te}$) gives unsatisfactory results (80JOM173).

A new method for the synthesis of cyclic iodonium ylides **484** has been developed via $\text{Rh}_2(\text{OAc})_4$ -catalyzed decomposition of α -diazodicarbonyl compounds and intramolecular capture of carbenes by aryl iodides (93MI2).

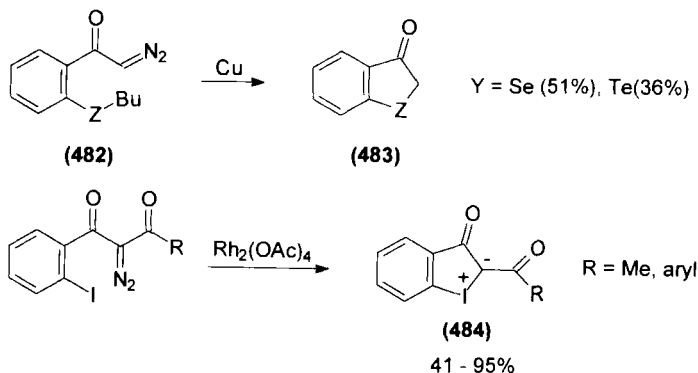
VII. Synthesis of Rings with Two Heteroatoms

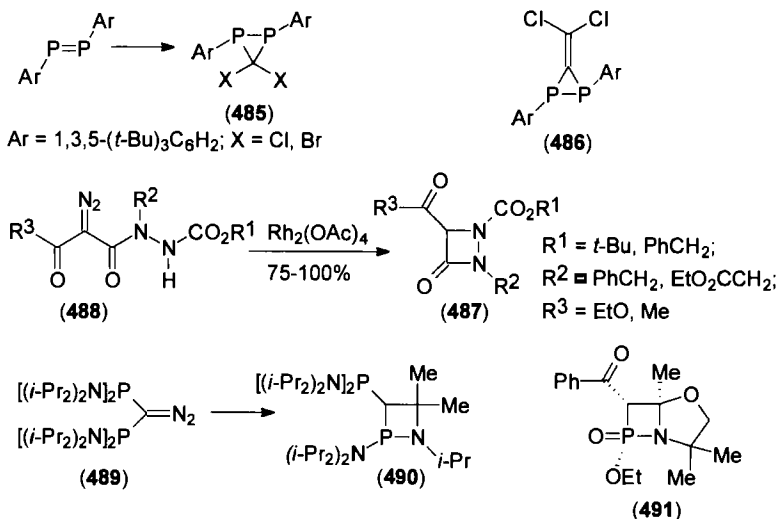
A. THREE- AND FOUR-MEMBERED RINGS

Diphosphiranes **485** were quantitatively obtained from diphosphenes and dihalogenocarbenes generated under sonochemical conditions from haloform and excess potassium hydroxide (91TL5965). Reaction of dichlorocarbene with a corresponding substituted diphosphaallene gives methylenediphosphirane **486** (91CC124). The reaction occurs via addition of a carbene to the $\text{C}=\text{P}$ bonds, followed by rearrangement of the intermediate formed by a way that is similar to the isomerization of methylene *gem*-dichlorocyclopropane.

Diazetidinones **487** were obtained in high yield (75–100%) by the decomposition of diazo compounds **488** in the presence of $\text{Rh}_2(\text{OAc})_4$ in refluxing benzene. This result is rationalized in terms of an intramolecular carbenoid insertion into the γ -NH bond [85TL3171; 87JCS(P1)899].

Carbene species, generated by thermolytic, photolytic, or $\text{Rh}(\text{II})$ -catalyzed decomposition of α -diazo- β -ketophosphonatoamidates **489**, insert into the tertiary $\text{C}-\text{H}$ bond of an *N*-isopropyl group to give 1,2-

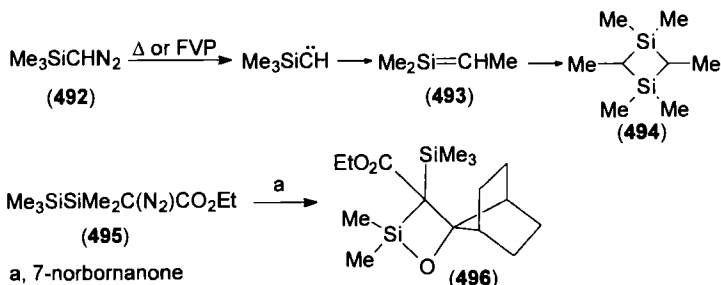




azaphosphetidines **490** in low yields. Compound **491** was prepared in an analogous way (90PS327; 92CC285).

A series of four-membered Si- or P-containing heterocycles was produced in various yields by electrocyclization or [2+2]-dimerization of compounds with multiple carbon-silicon or carbon-phosphorus bonds. These unsaturated species are formed under photolysis of diazo compounds containing a P or Si atom in an α position with respect to the diazo group, following a [1,2]-sigmatropic shift in the intermediate carbene.

It was reported that trimethylsilyldiazomethane **492** thermolytically (440°C, 10 torr) (75TL2061) or under FVP conditions (750°C) (86JA7849) produces a carbene that isomerizes to 1,1,2-trimethylsilene **493**, thereby furnishing the head-to-tail dimer **494** in 40% yield. Silene generated from disilanyl α -diazoacetate **495** in the presence of 7-norbornanone affords 38% of adduct **496** (82JA6830).



Photolysis of disilanyl α -diazoketones **497** leads through the sequence involving silyl carbene formation followed by rearrangement to acyl silenes and their facile cyclization to give 1-oxa-2-sila-3-cyclobutenes **498** (84JA1486; 88CC72; 90CB589).

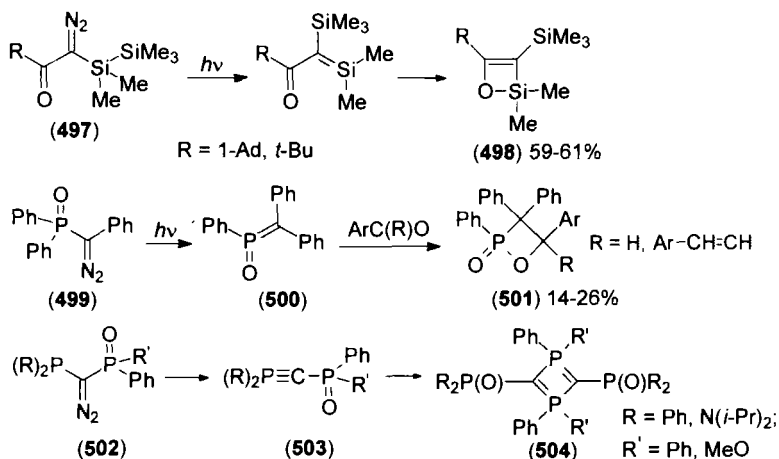
The carbene generated by photolysis of diazo compound **499** rearranges via phenyl migration to a short-lived phosphene **500**, which with aldehydes or ketones gives [2+2]-cycloadducts (λ^5 -1,2-oxaphosphetanes (**501** (80CB3303; 81T1039).

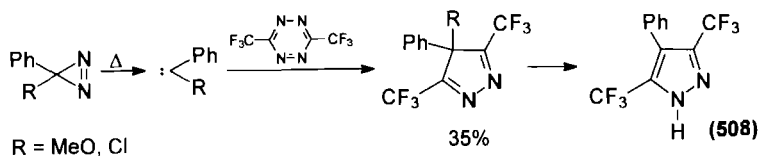
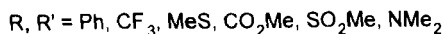
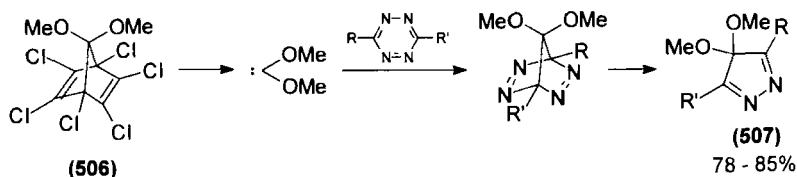
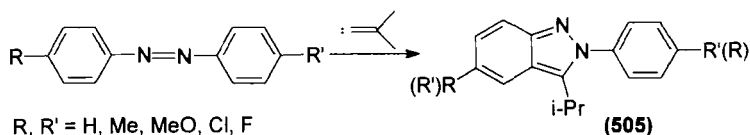
Diazo compounds **502** generated by the reaction of chlorophosphines with silver diazo compounds undergo spontaneous decomposition into λ^5 -1,3-diphosphetes **504**. Formation of the latter can be rationalized by the intermediacy of $\lambda^5\sigma^3$ -phosphaalkynes **503** followed by dimerization and a P \rightarrow P oxygen shift [85ZN(B)1258; 86TL1903].

B. FIVE-MEMBERED RINGS

1. Heterocycles with Two Nitrogen Atoms

There are only a few examples of carbene reactions that afford pyrazole derivatives. First, we mention the reaction of azobenzene with isopropylidenecarbene, which proceeds via an azomethine imine and its cyclization in indazole system **505**. In the case of the unsymmetrically substituted azobenzenes, both isomeric products were obtained (77JA2597; 84JA6015). Isopyrazoles are accessible via a convenient route with nucleophilic carbene



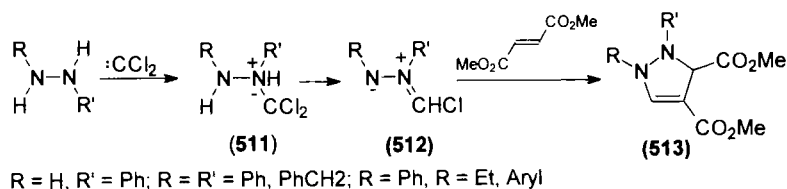
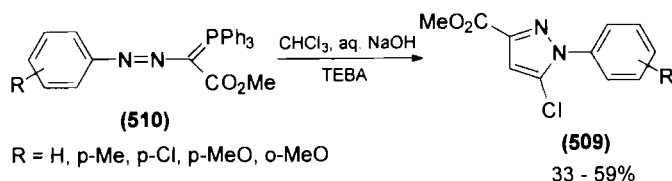


intermediacy (87CZ9). For example, dimethoxycarbene generated from norbornadienone ketal **506**, reacts in a [4+1]-cycloaddition with 1,2,4,5-tetrazines. The subsequent [4+2]-cycloreversion affords 4,4-dimethoxyisopyrazoles **507** in high yields (91TL2743; 93CB733). Notably, this reaction may also be carried out with ambiphilic carbenes such as methoxyphenylcarbene and phenylchlorocarbene when active bis(trifluoromethyl)-substituted tetrazine is used. Chloro-substituted isopyrazole is unstable, giving 33% of pyrazol **508** after hydrolysis and a 1,3-H-shift.

One unusual approach to the synthesis of pyrazoles **509** from azo compounds **510** under phase-transfer conditions for the generation of dichlorocarbene was proposed by Baldoni *et al.* (89JHC241).

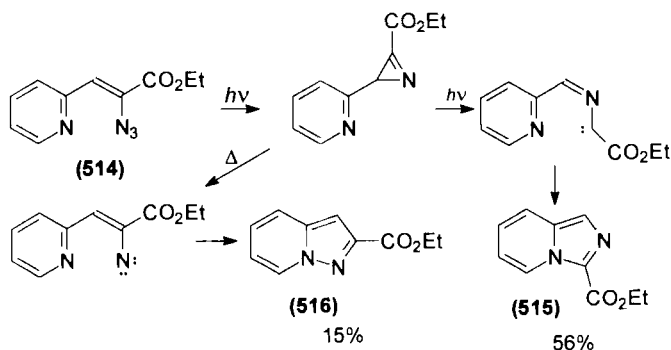
An interesting reaction was observed on phase-transfer generation of dichlorocarbene in the presence of mono- and 1,2-disubstituted hydrazines and dimethyl maleate. In this case the initially formed ammonium ylide **511** transforms to azomethine imine **512** followed by 1,3-dipolar cycloaddition to an olefin providing pyrazolines **513** 96ISV(ip).

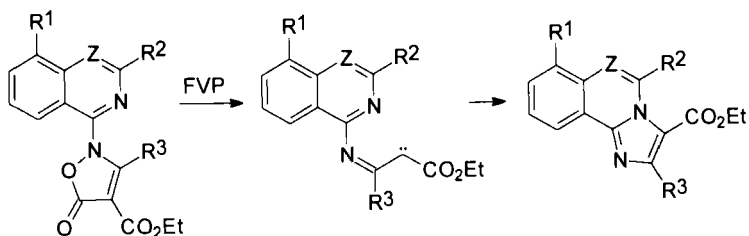
In contrast to the synthesis of pyrazoles, carbene synthetic approaches to imidazoles are highly diversified. Photolytic reactions of 2*H*-azirines provide one of the well-known synthetic methods. When irradiated, these compounds undergo irreversible C—C bond cleavage to give nitrile ylides capable of reacting as 1,3-dipoles or as arylideneaminocarbenes both inter-



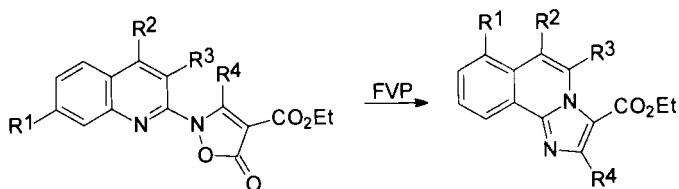
and intramolecularly (76ACR371; 80H1517). In this way, 2-imidoazirines transform to imidazole derivatives (75S483). Photolysis of azide **514** gives imidazopyridines **515** together with a small amount of pyrazolopyridine **516** [86JCS(P1)1119]. Mechanistically, this reaction includes the formation of azirine, which can then undergo both C—C bond cleavage (“photolytic” cleavage), affording **515**, and C—N bond cleavage (“thermal” cleavage), yielding **516**.

One more convenient method for annelating an imidazole ring to various nitrogenated heterocycles is based on a carbene 6π -cyclization. The approach, shown in Scheme 29, consists in introducing of an oxazolone moiety (serving as a carbenoid center) into a heterocycle, followed by flash vacuum pyrolysis (FVP). This leads to an iminocarbene, which then undergoes 6π -cyclization to produce fused imidazoles in excellent yields (92AJC1811; 93T8147).

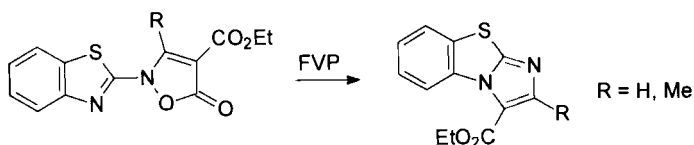




Z = N, CR⁴; R¹, R², R³ = H, NO₂; R⁴ = H, Me



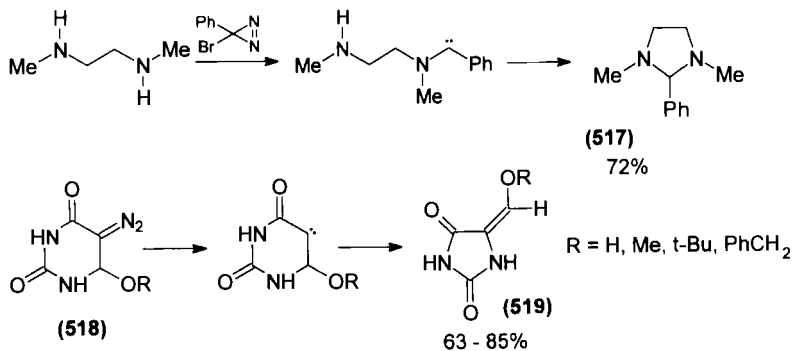
R¹, R², R³, R⁴ = H, Me, MeO, Ph, Cl; R⁴ = H, Me



R = H, Me

SCHEME 29

Moss *et al.* succeeded in producing imidazolidine **517** by a one-pot procedure involving alkylation of *N,N'*-dimethylethylenediamine with 1-bromo-1-phenyldiazirine, carbene generation, and subsequent cyclization (84TL1023). Rh₂(OAc)₄-catalyzed composition of diazo uracils **518** affords good yields of imidazolidinones **519** via carbenoid ring contraction



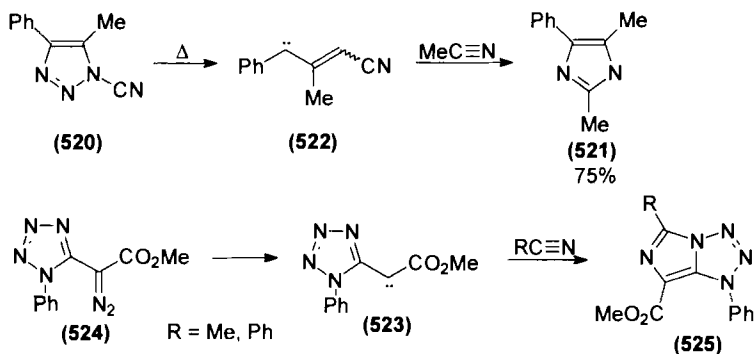
(91TL3799). It is to be noted that this reaction is impractical with 5-diazo-6-(*N,N*-disubstituted amino)- and 6-(substituted thio)dihydrouracils owing to a 1,2-shift of the functional group in the intermediate carbene, which results in 5-substituted derivatives.

Thermolysis of triazole **520** in acetonitrile affords imidazole **521** in 75% yield. Its formation was rationalized in terms of a 1,3-dipolar cycloaddition of the intermediate α -cyaniminocarbene **522** to the $C\equiv N$ bond of the solvent [81AG(E)113], although the mechanism of ylide formation with concomitant cyclization must not be ruled out. The similar nitrile with carbene **523**, generated from diazo tetrazole **524**, leads to imidazotetrazolic systems **525** ($R = \text{Me, Ph}$) in 42 and 51% yield, respectively (85T4621).

A further route to annelating the imidazole ring involves the reaction of dihalogenocarbenes with 2-functionalized azines. 1,5-Cyclization of pyridinium ylides **526**, generated by dichlorocarbene addition to pyridines **527**, produces imidazo[1,2-*a*]pyridines **528** in 41–81% yields. A change to 2-(benzylideneamino)quinoline, less favorable to ylide formation with dichlorocarbene, reduces the yield of annelation product. The structures of the isolated by-products point to an appreciable contribution from competitive dichlorocarbene reactions with both the starting quinoline **527** and the final imidazo[1,2-*a*]quinoline. Khlebnikov *et al.* also succeeded in constructing the 1-bromo-substituted imidazo[1,2-*a*]pyridine system through the reaction of pyridines **527** with dibromocarbene generated under phase-transfer conditions, the yield being, however, lower than with dichlorocarbene (91KGS810).

Reacting dichlorocarbene with aminomethyl-substituted azines **529** and **530** provides access to imidazo[1,5-*a*]pyridine and imidazo[5,1-*a*]isoquinoline in moderate yields, even though dichlorocarbene is not the reactant of choice for such transformations (91JOC2400).

An interesting route to the imidazolidine ring exploits a reaction of dichlorocarbene, generated by the action of potassium *tert*-butoxide on

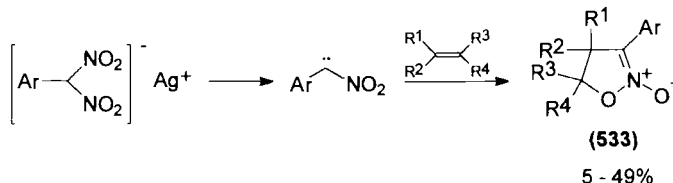


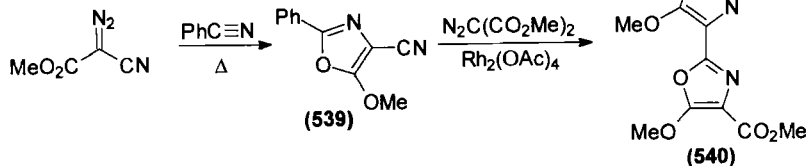
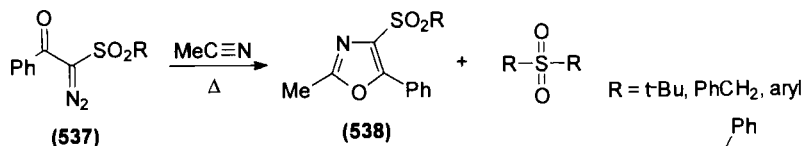
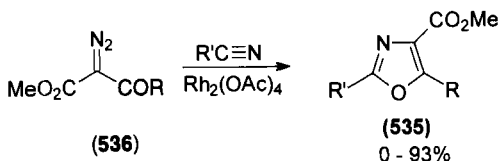
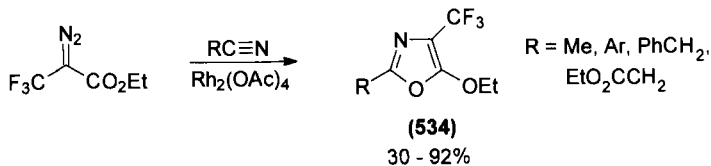
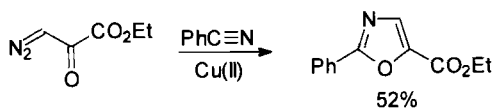
low yields, are also found in reactions of azobenzene with dichlorocarbene (85BCJ1055) and dimethylvinylidenecarbene (75H193).

2. Heterocycles with One Nitrogen and One Oxygen Atom

With isoxazole derivatives, carbene reactions are of virtually no synthetic value. The only exception affords Δ^2 -isoxazoline *N*-oxide **533** in moderate yields by thermal decomposition of the silver salt of aryldinitromethanes in the presence of electron-rich alkenes. This synthesis involves 1,3-dipolar cycloaddition of the intermediate arylnitrocarbenes to the olefins (80JOC4158).

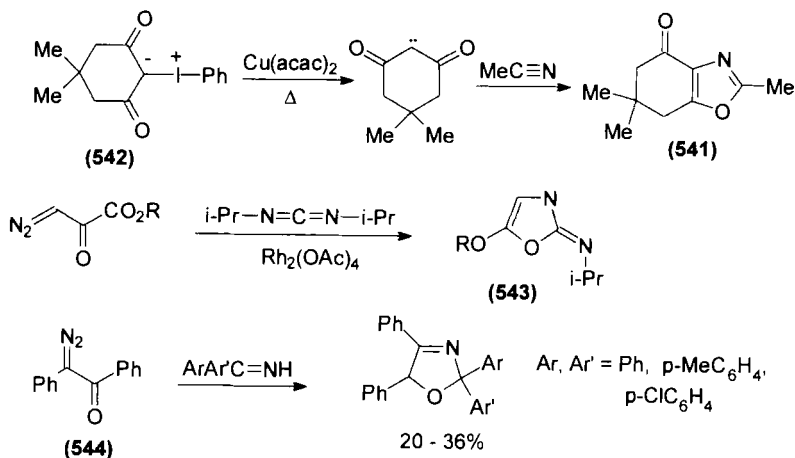
The reaction of carbenes with nitriles is the most frequently encountered method for constructing the oxazole ring. Diazocarbonyl and diazodicarbonyl compounds are the most common precursors of carbenes in these reactions. Ring formation is proposed to occur via a nitrile ylide, followed by 1,5-cyclization with the participation of a carbonyl oxygen of the initial diazo compound. An example is the Cu-catalyzed reaction of ethyl diazopyruvate with benzonitrile (80JHC721). One attractive method for the preparation of trifluoromethyl-substituted oxazoles is based on the synthetically available 3-trifluoro-2-diazopropionate anion. The advantage of this reaction is that the Rh(II) carbenoid generated is able to add to a wide range of nitriles, giving **534** in high yields (89CC607). The reaction of Rh(II) carbenoid derived from dimethyl diazomalonate furnishes high yields of oxazoles **535** ($R = CO_2Me$) with aromatic nitriles and good yields with aliphatic nitriles (86TL5559; 92TL2159; 93T5445). However, no cyclic products were obtained with deactivated nitriles such as *p*-nitrobenzonitrile. When the nitrile contains an activated multiple bond, the reaction yield is diminished due to competitive cyclopropanation; however, a hydroxy group directs the reaction to exclusive formation of O—H insertion products. In the reaction of **536** ($R = H$), containing two different carbonyl groups, ring formation takes place with the participation of the more highly polarized aldehyde group, affording 4-carboxy-1,3-oxazoles (91TL17; 92JOC4797), which are useful intermediates in the synthesis of natural products (90MI1).





Carbene obtained by thermolysis of diazo sulfone **537** reacts with acetonitrile, used as a solvent, to give oxazole **538** (83CPB526). Likewise, ethyl α -phenylsulfodiazooacetate with nitriles furnishes good yields of oxazoles (92TL7769). Doyle and Moody proposed cyano-substituted α -diazo esters as starting compounds in the synthesis of bisoxazoles. By treating methyl diazocynoacetate with Rh₂(OAc)₄ in the presence of benzonitrile, they obtained 4-cyanoxazole **539** in 35% yield. In order to construct the second oxazole ring, the latter was introduced in a reaction with dimethyl diazoacetate using Rh(II) trifluoroacetamide as a catalyst, thereby producing bisoxazol **540** in 53% yield (92TL7769).

This type of transformation forms the basis of the approach to polyoxazoles elaborated by Yoo (92TL2159). A good yield of oxazole **541** was obtained by using phenyliodonium dimedonate **542** as a carbene precursor in a reaction with acetonitrile (87TL4449).

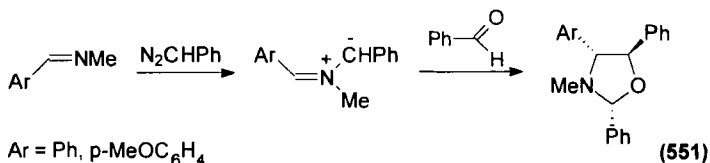
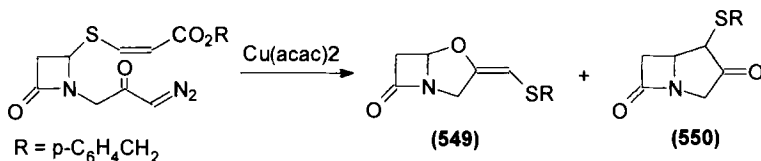
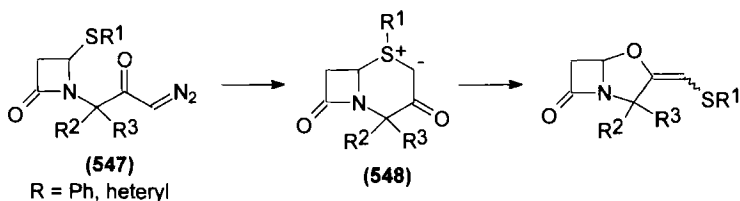
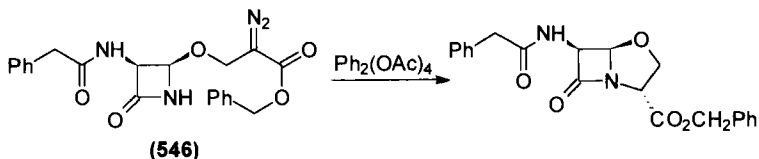
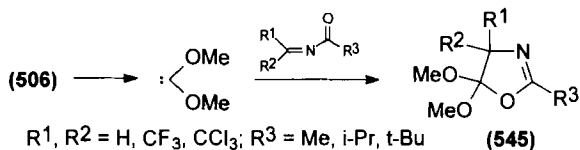


Reactions of carbenes and carbenoids from diazocarbonyl compounds with substrates containing a $\text{C}=\text{N}$ bond usually furnish oxazolines. *N,N'*-Diisopropylcarodiimide reacts with carbenoids derived from alkyl diazoacetates in the presence of transition-metal salts to give oxazolines **543** (79TL559), which were originally mistaken for 1-isopropyl-2-alkoxycarbonyl-3-isopropyliminoaziridines (76TL1317). Prasad and Mehrotra described a convenient single-step route to Δ^3 -oxazoline from the $\text{Cu}(\text{acac})_2$ -catalyzed decomposition of 2-diazo-1,2-diphenylethanone **544** in the presence of substituted benzophenone imines (82JOC2806).

The imine reaction with carbenes is also efficient when the carbonyl group participating in oxazoline ring formation is incorporated in an imine, rather than a carbene, component. This is exemplified by a reaction of dimethoxycarbene with acylimines, resulting in good yields of substituted oxazoles **545**, as well as by a reaction of difluorocarbene with imine **13**, affording oxazoline **14** in 62% yield (79IZV1826).

Intramolecular $\text{N}-\text{H}$ insertion of Rh carbenoid from diazo compounds may be applied when annelating oxodiazolidine to a β -lactam ring. Cyclization of diazo compound **546** was the key step in the total synthesis of β -lactam antibiotic (\pm)-1-oxabisnorpenicollin G (78TL4233).

One more carbene-based route to oxapenam derivatives utilizes the Cu-catalyzed decomposition of diazo compounds **547** via cyclic sulfonium ylide **548**. The protocol is effective for *S*-aryl (80H1999) and *S*-heteryl-substituted (82H1597) diazo compounds of type **547**. Oida and co-workers succeeded in obtaining oxapenam **549** (33%) by $\text{Cu}(\text{acac})_2$ -catalyzed transformation of *S*-alkenyl-substituted diazo ketones **550**. The attempted synthesis of



alkylthio analogs under these conditions has failed, providing only C—H insertion products (80H1999).

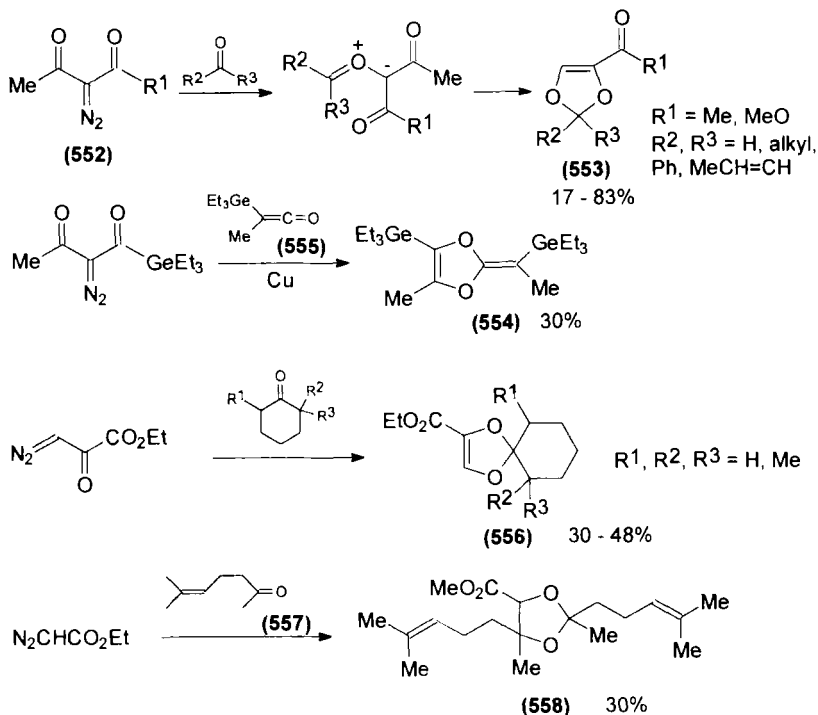
The three-component reaction of *N*-benzylidenemethylamine with phenyldiazomethane and benzaldehyde proceeds via an azomethine ylide, which is stabilized by 1,3-dipolar addition to an aldehyde, furnishing oxazolidine **551** (84T2569).

3. Heterocycles with Two Oxygen Atoms

The only known carbene approach to dioxolane derivatives exploits carbene reactions with carbonyl-containing compounds. The mechanism of

this reaction, having been long debated (80JHC721), now is believed to involve the initial formation of a carbonyl ylide, which then undergoes either 1,5-cyclization with the participation of the carbonyl group of a diazo compound or intermolecular [3+2]-cycloaddition. The way in which the ylide is further stabilized is controlled by both the structure of the initial carbonyl compound and the nature of carbene or carbenoid. The copper-catalyzed decomposition of methyl 2-diazo-3-oxobutyrates **552** ($R^1 = \text{MeO}$) and 3-diazopentane-2,4-dione **552** ($R^1 = \text{Me}$) in the presence of aldehydes and ketones proceeds smoothly via 1,5-cyclization of a transient carbonyl ylide with exclusive formation of dioxoles **553** in moderate to high yields. In these reactions, $\text{Cu}(\text{hfacac})_2$ is found to be the catalyst of choice (81TL4181; 85JOC3445).

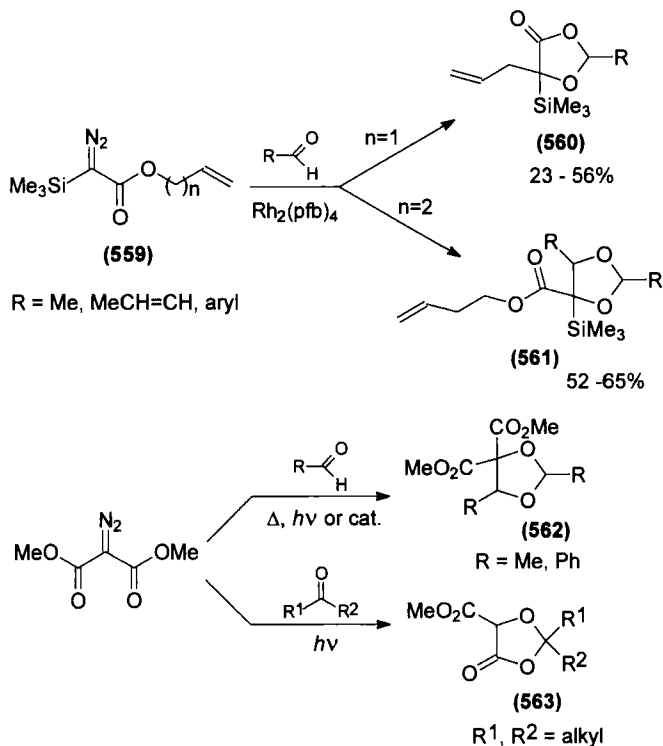
Within the framework of the above methodology, 2-methylenedioxole **554** is accessible by trapping a carbene with ketene **555** (77JOM155). Ethyl diazoacetate reacts with substituted cyclohexanones in the presence of $\text{Cu}(\text{acac})_2$ in a similar manner to produce spirodioxoles **556** (80JHC721), while the reaction of ethyl diazopyruvate with ketone **557** furnishes the 1:2 adduct **558** [88CI(L)631].



A similar change of mechanism is observed in the reaction of silyl-substituted diazo esters **559** with acetaldehyde and benzaldehyde. The $\text{Rh}_2(\text{pfb})_4$ -induced decomposition of allyl ester **559** ($n = 1$) in the presence of a carbonyl compound yields 1:1 adducts **560**, whereas homoallyl ester **559** ($n = 2$) under the same conditions produces only 1:2 adducts **561** (94CB1537).

Carbenoids derived from dimethyl diazomalonate usually react with aldehydes via 1,3-dipolar cycloaddition of the intermediate carbonyl ylide, yielding dioxolanes **562** (82JA4953; 88JA209). As was shown by Huisgen and de March, any one of the Cu(I), Cu(II), and Rh(II) catalysts may be used to advantage in reactions with benzaldehyde. Diminished yields are observed with free bis(methoxycarbonyl)carbene, generated by thermolysis of dimethyl diazomalonate, owing largely to the competitive 1,3-cyclization of the carbonyl ylide to an oxirane (82JA4953). The reaction of this carbene, generated by photolysis of a diazo diketone, with acetaldehyde gives similar results; but with ketones, only 1:1 adducts **563** are formed (88JA209).

Reactions of other carbenes with carbonyl compounds, resulting in the formation of dioxolanes, have received much less study. Dimethoxycarbene,



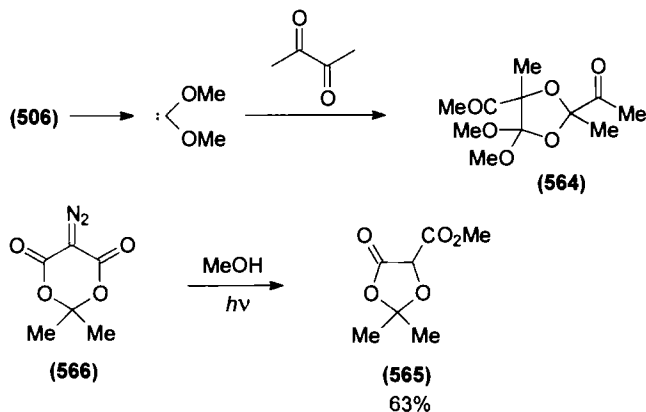
generated from **506**, with butane-2,3-dione produces dioxolane **564** in 57% yield. Dioxolane derivatives are also formed in reactions of arylchlorocarbenes with aldehydes and ketones, which were thoroughly studied by Liu and co-workers (87CL2135).

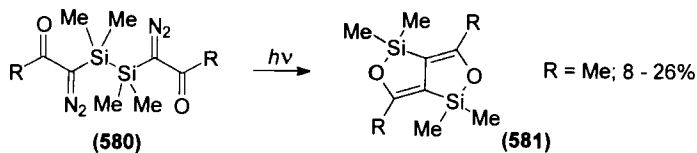
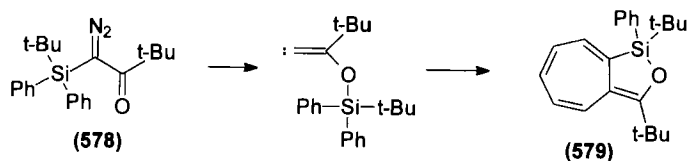
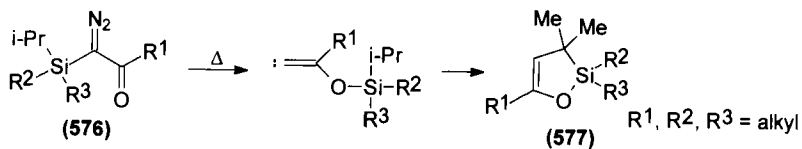
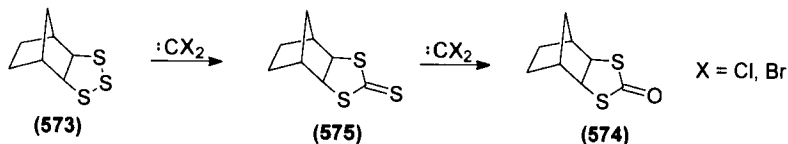
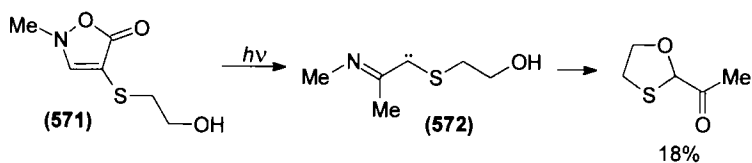
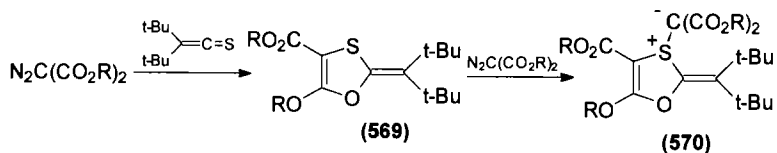
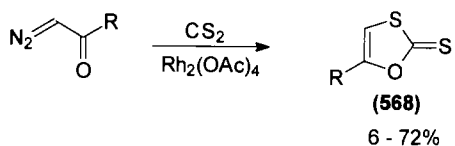
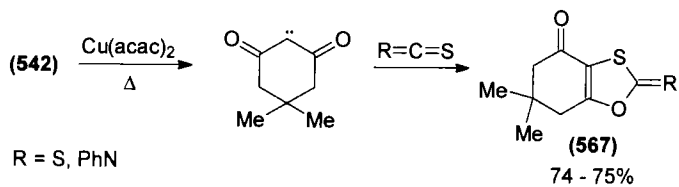
1,3-Dioxane ring contraction via Wolff rearrangement is the basis of the synthesis of dioxolane **565** by photolysis of diazo diketone **566** in methanol (85KGS321).

4. Other Five-Membered Heterocycles

The synthetic approach to oxathioles, which is generally analogous to the above methods for oxazoles and dioxoles, involves the interactions of ketocarbenes with compounds containing a C=S bond. Good results with oxathioles **567** were obtained by Hadjiarapoglou, who carried out the reactions of phenyliodonium dimedonate with carbon disulfide and phenyl isothiocyanate in the presence of $\text{Cu}(\text{acac})_2$ (87TL4449). Diazo ketones are also effective as precursors of Rh(II) carbenoids in the reactions with CS_2 , leading to 1,3-oxathiones **568** (89MI1). Ando and co-workers (89TL1249) have reported the addition of diketocarbenoids to the ketene C=S bond. They have succeeded in producing oxathiole **569** in 66% yield by the reaction of di-*tert*-butylthio ketene with dialkyl diazomalonate in the presence of $\text{Rh}_2(\text{OAc})_4$. Treatment of thio ketene with excess diazo compound affords sulfonium ylides **570** in moderate to good yields. The formation of oxathiole was detected in the photolysis of S-substituted isoxazolin-5-one **571**, which occurs via iminocarbene **572** (80CC1054).

Trithiolanone **573** with dichloro- and dibromocarbene, generated under phase-transfer conditions, produces dithiolanone **574** in 60% yield. The reaction proceeds via isolable dithiolanethione **575** (90JOC1146).





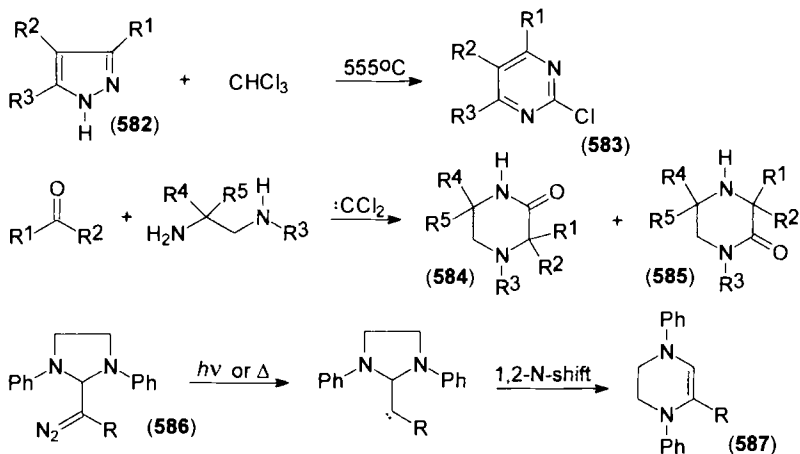
Maas and co-workers have elaborated the approach to 1-oxa-2-silacyclopentene derivatives based on cyclization of a siloxyalkylidenecarbene. Thus, as a result of intramolecular aliphatic C—H insertion of the carbene derived from diazo ketone **576**, 1-oxa-2-sila-4-cyclopentenones **577** were obtained in high yields. Here, the insertion may occur in primary, secondary, and tertiary C—H bonds (87CB635; 94JOM115). When no C—H bond is adjacent to the Si atom, as in substrate **578**, the cyclopropanation of a benzene ring with concomitant ring expansion may result in oxasilacyclopentene **579** (86CC1782). Photolysis or catalytic decomposition of bissilanes **580** furnishes fused bicyclic heterocycles **581** in moderate yields (90JOM229).

C. SIX-MEMBERED RINGS

1. Heterocycles with Nitrogen and Another (N, O, S, Si) Atom

Carbene reactions have not been widely utilized for the synthesis of six-membered heterocycles containing two nitrogen atoms.

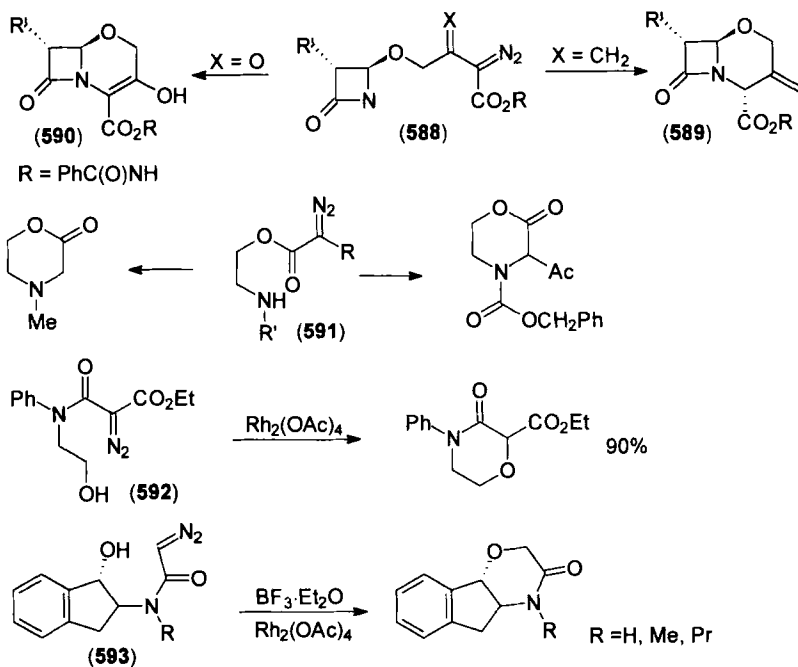
The reaction of dichlorocarbene generated under phase-transfer conditions with 2,4,5-trimethylimidazole gives 39% of 5-chloro-2,4,6-trimethylpyrimidine. 3,4,5-Trimethylpyrazole produces under the same conditions only 2.7% of 4-chloro-3,5,6-trimethylpyridazine, tris(1*H*-3,4,5-pyrazol-1-yl)-methane (63%) being the major reaction product (76S798). By contrast, dichlorocarbene generated by vapor-phase thermolysis of chloroform upon reacting with pyrazoles **582** ($R^1, R^2, R^3 = H, Me$) affords 2-chloropyrimidines **583** in 51–89% yields. Under the same conditions, indazole provides 66% of 2-chloroquinazoline [79JCS(P1)2786].



The reaction of dichlorocarbene with ketones and diamines results in near quantitative formation of a mixture piperazinones **584** and **585** (80JOC754). As shown in Section III,C,2, piperazine **78** [$R = H$, $R' + R' = (CH_2)_5$], the minor product of the $Rh_2(OAc)_4$ -catalyzed decomposition of diazo ester **73**, is the result of the dimerization of the intermediate ylide **76** (84JOC113). Tetrahydropyrazines were synthesized through ring expansion of imidazolidines. Thermolysis or photolysis of diazo compounds **586** [$R = CO_2Me$, $PhC(O)$, $Ph_2P(O)$] yields the corresponding pyrazines **587** (thermolysis 40–59%; photolysis 11–25%) (85BSB499).

The formation of 1,3- and 1,4-oxazine rings in carbene reactions involves, almost without exception, nitrogen or oxygen atoms. Intramolecular carbenoid insertion into an N–H bond was employed for constructing the 1,3-oxazine ring. The ring closure of diazo- β -keto esters **588** ($X = CH_2$, $R = Ph_2CH$; $X = O$, $R = t-Bu$, $p-NO_2C_6H_4CH_2$) was achieved using rhodium(II) acetate catalysis to give 1-oxacepham **589** ($R = Ph_2CH$) in 53% yield (84TL4545) or 3-hydroxyoxacephams **590** ($R = t-Bu$, $p-NO_2C_6H_4CH_2$) in 82 and 61% yield, respectively (84T3667).

The $Rh_2(OAc)_4$ -catalyzed N–H insertion of carbenoids derived both from diazo ketone **591** ($R = H$, $R' = Me$) and from diazo ketone **591** ($R = Ac$, $R' = PhCH_2OCO$) furnishes the corresponding 1,4-oxazines in



low yields (83IZV1933; 85JOC5223). By contrast, diazo keto ester **591** ($R = CO_2Et$, $R' = PhCH_2OCO$) produces no N—H insertion product (85JOC5223).

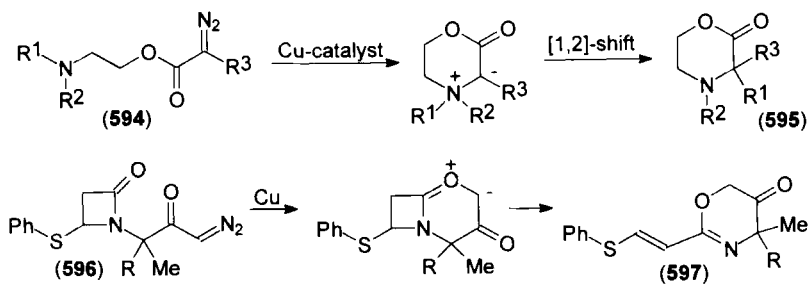
The intramolecular carbenoid O—H insertion accompanying decomposition of diazo keto ester **592** leads, however, to the formation of the corresponding 1,4-oxazine derivative in 90% yield (94JOC2447). Similarly, the tetrahydroindeno[1,2-*b*]-1,4-oxazin-3(2*H*)-one system was stereoselectively synthesized via $BF_3 \cdot Et_2O$ - or $Rh_2(OAc)_4$ -catalyzed ring closure of β -hydroxydiazoacetamides **593** (83JOC2675).

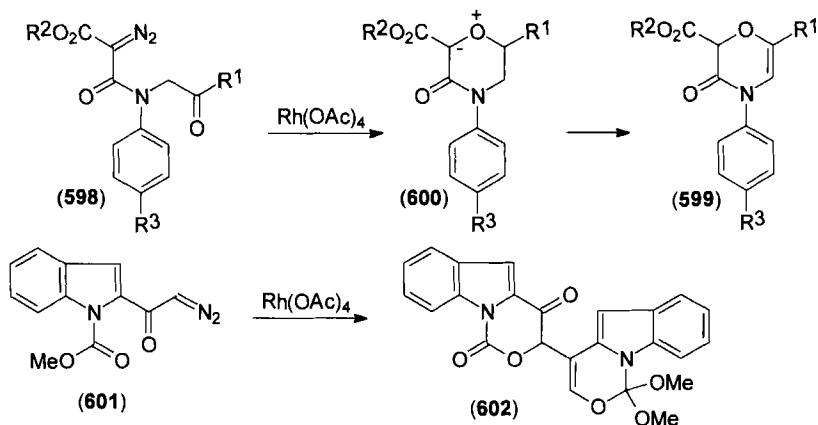
The overall sequence of copper-catalyzed generation/ammonium ylide formation/Stevens [1,2]-shift utilizing acyclic 2-(*N,N*-dialkylamino)ethyl diazoacetates can be applied to the synthesis of morpholinones. In most cases involving benzylic or allylic migrating groups, when refluxed in toluene in the presence of catalytic Cu, diazoacetates **594** ($R^1 = p\text{-}R\text{-}C_6H_4CH_2$, $H_2C=CHCH_2$, $Me_2C=CHCH_2$; $R^2 = Me$, $H_2C=CHCH_2$; $Me_2C=CHCH_2$; $R^3 = Ac$) cleanly form the corresponding morpholinones **595** (55–80%). Simple alkyl groups failed to undergo the rearrangement, with the exception of the *tert*-butyl case **594** ($R^1 = t\text{-}Bu$, $R^2 = Me$, $R^3 = Ac$), which furnishes the corresponding **595** in 10% yield. Diazoacetates **594** ($R^1 = NCCH_2$, $PhCH_2$; $R^2 = Me$, $PhCH_2$; $R^3 = H$) also undergo conversion to **207** in 19–64% yield with $Cu(acac)_2$ catalysis (94JOC6051).

1,4-Oxazine-ring formation occurs by carbenoid cyclization to produce pyridinium ylide, which is then intercepted by a dipolarophile (see Scheme 21) (93JOC1144).

An intramolecular cyclization of a carbenoid to a six-membered carbonyl ylide followed by its rearrangement provides access to both 1,3- and 1,4-oxazine derivatives. Thus, the Cu-mediated reaction of diazo compound **596** ($R = Me$, CO_2Me) gives the corresponding 1,3-oxazinone **597** in 48 and 59% yield, respectively (80H1999).

The rhodium(II) acetate-catalyzed decomposition of diazo ester **598** ($R^1 = Ph$, $R^2 = Et$, $R^3 = H$) furnishes 1,4-oxazinone **599** in 77% yield via a





hydrogen-shift rearrangement of the initial carbonyl ylide **600** (94JOC2447). Similarly, diazo ester **598** ($R^1 = t\text{-BuO}$, $R^2 = \text{Me}$, $R^3 = \text{MeO}$) affords 42% of the corresponding **599** along with 39% of methyl 4-(methoxyphenyl)-3,6-dioxo-3,4,5,6-tetrahydro-2*H*-1,4-oxazinecarboxylate arising from loss of the *tert*-butyl group (92JOC4404).

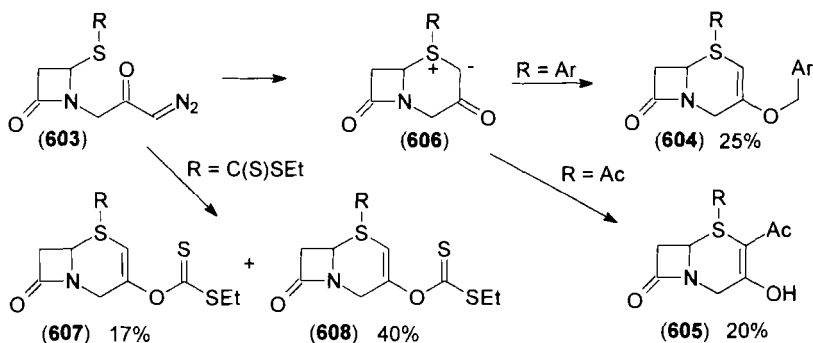
The interception of the transient rhodium carbenoid formed from diazo compound **601** by a carbonyl oxygen produces carbonyl ylides that, upon dimerization and subsequent rearrangement, give 56% of compound **602** (92JA593).

A 1,3-oxazine ring incorporated into a tricyclic ring system was constructed from **96** as a result of applying a dipole-cascade/[3+2]-cycloaddition methodology (see Scheme 21) (93JOC1144).

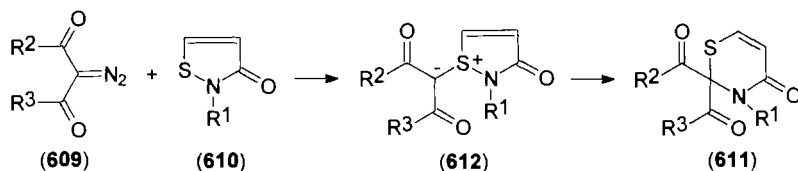
The overall sequence of carbenoid generation/ylide formation/[3+2]-cycloaddition or rearrangement was explored in the synthesis of a series of 1,3-triazine derivatives. Thus, 1,3-dipolar cycloaddition of the pyridinium ylide derived from 2-(3-diazo-2-oxopropylthio)pyridine gives a 1,3-thiazine ring incorporated into the polycyclic system (Scheme 21) (93JOC1144).

The metal-catalyzed decomposition of diazo compounds **603** provides access to a variety of cephem derivatives (Scheme 30). Copper-mediated cyclization of diazo ketone **603** ($R = \text{Et}$) gives 3-oxocepham through sulfonium ylide formation followed by β -elimination (80H1999). The formation of cephem derivatives **604** and **605** presumably involves the intermediacy of ylide **606** ($R = \text{Ac}$, ArCH_2) and its subsequent rearrangement. A more sophisticated mechanism is proposed for the formation of **607** and **608** (83H205).

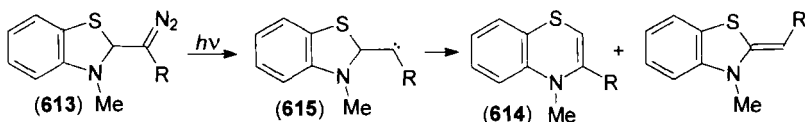
The rhodium(II) acetate-catalyzed addition of diazo compounds **609** to isothiazolones **610** results in a ready conversion into 1,3-thiazinones **611**



SCHEME 30



$R^1 = \text{Et}, \text{CO}_2\text{Me}; R^2 = R^3 = \text{OMe}; R^2 = \text{Me}, \text{OEt}; R^2 + R^3 = \text{OCMe}_2\text{O}, o\text{-C}_6\text{H}_4$



$R = \text{PhC(O)}, (\text{MeO})_2\text{P(O)}, \text{Ph}_2\text{P(O)}$

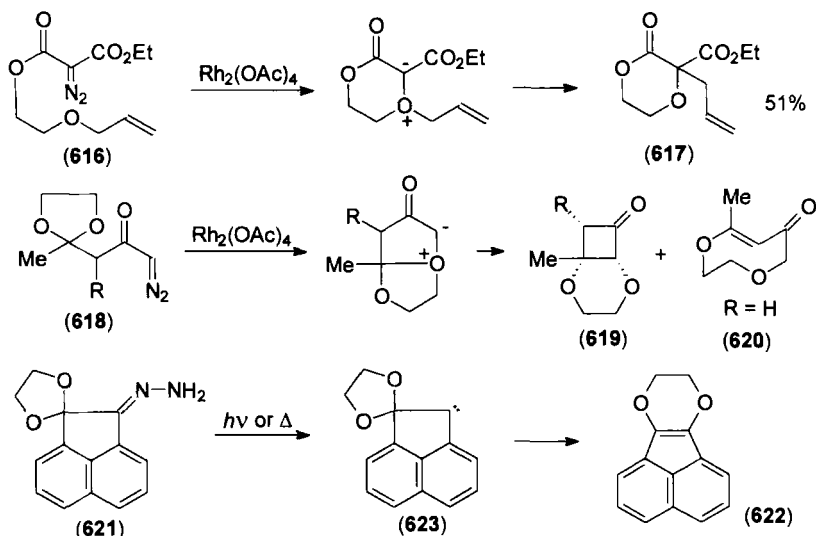
in 58–95% yield. A mechanism for this conversion involves trapping the carbenoid to form an intermediate sulfonium ylide **612**, which undergoes ring expansion by a [1,2]-shift (83CC643).

Photolysis of diazo compounds **613** yields 1,4-benzothiazines **614** (15–30%) by a [1,2]-N-shift of the carbene intermediates **615** along with methylenbenzothiazolines (23–42%) by [1,2]-H-shift (85BSB499).

2. Other Six-Membered Rings

The generation of oxonium ylides by decomposition of malonate **616** followed by a [2,3]-sigmatropic shift affords dioxane **617** (86JA6060). Similarly, rearrangement of the oxonium ylide derived from **618** ($R = \text{H}$ or Me) gives 68% of dioxane **619** ($R = \text{H}$) and 16% of 1,4-dioxacyclooctane **620** or dioxane **619** ($R = \text{Me}$) as a sole diastereomer (86JA6062).

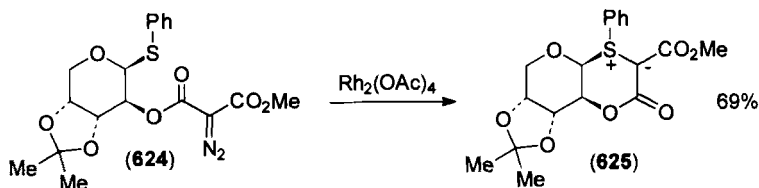
Photolysis or thermolysis of **621** results in dioxin **622** (51 and 31%, respectively), the product of migration of one of the acetal oxygen moieties in

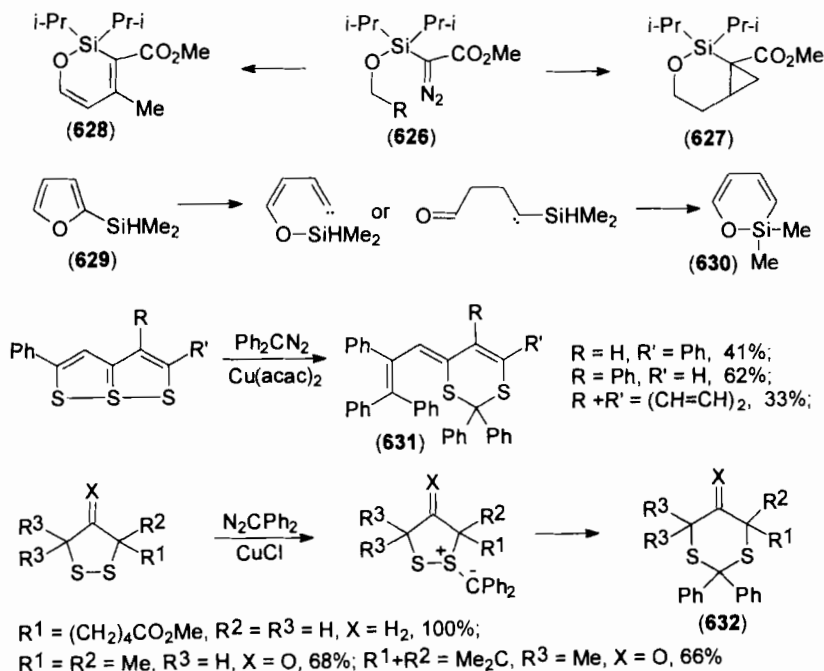


carbene intermediate **623** (82JOC4226). The formation of stable cyclic six-membered O- and S-containing ylides in carbene reactions is unusual. Intramolecular reaction of **624** gives the isolable ylide intermediate **625**, whose structure was determined by X-ray analysis (87JA3010).

(Butenyloxy)diazoacetic ester **626** ($\text{R} = \text{H}_2\text{C}=\text{CHCH}_2$) undergoes intramolecular cyclopropanation to form **627** (28–58%) when decomposed photochemically, thermochemically, or by transition-metal catalysis ($\text{CuOSO}_2\text{CF}_3$). (Alkynyloxy)diazoacetic ester **626** ($\text{R} = \text{C}\equiv\text{CMe}$) under photolytic and catalytic conditions gives **628** resulting from tandem intramolecular cyclopropanation and cyclopropene–vinylcarbene isomerization (94MI1).

Flash vacuum pyrolysis of **629** affords **630** in 15% yield together with other products [85JA(107)8297]. The reaction of trithiapentalenes with diphenylcarbene gives sulfonium ylides that undergo rearrangement followed by formation of 1,3-dithiins **631** (83CJC1161). The carbenoid, generated by catalytic decomposition of diphenyldiazomethane, reacts with cyclic





disulfides, yielding 1,3-dithianes **632**. Under the same conditions, ethyl diazoacetate with 3,3,5,5-dithiolan-4-one also gives the corresponding dithiane as the product of a formal S—S insertion (85TL5187).

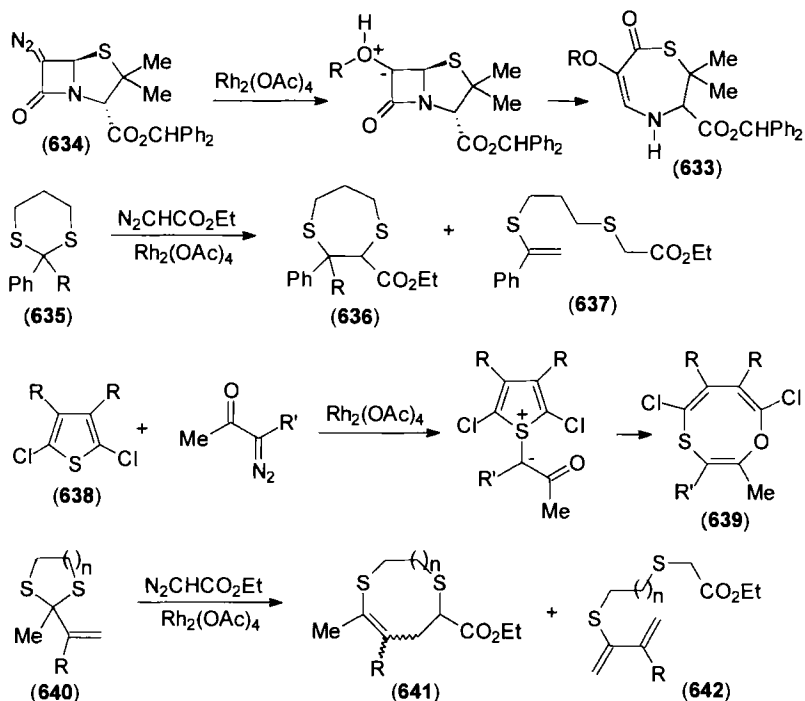
D. SEVEN-MEMBERED AND LARGER RINGS

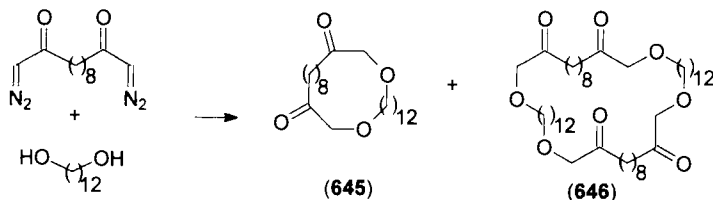
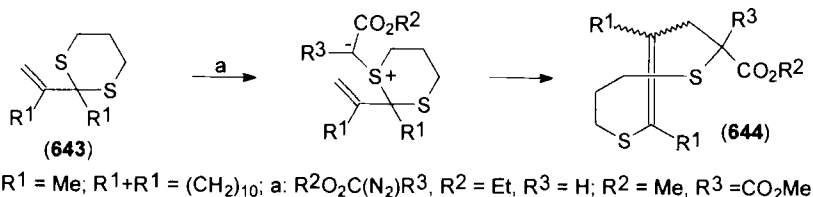
The literature is fairly scanty on the carbene approach to seven-membered and larger rings containing two heteroatoms. The above-mentioned decomposition of diazo compound **34** ($\text{R} = t\text{-Bu}$, Pr , $\text{R}' = \text{Et}$) can be directed to produce the corresponding 1,4-oxazepines **38** via an ester carbonyl entrapment of the intermediate carbenoid. The yield of **38** increases with the increasing power of the bridging ligands of the rhodium(II) catalyst, and it is greatest with $\text{Rh}_2(\text{pfb})_4$ (89TL5397; 91JOC820). Rearrangement of dimorpholinocarbene **188** ($\text{Z} = \text{O}$) furnishes 1,4-oxazepine derivative **189** ($\text{Z} = \text{O}$) in 70% yield (88JOC1806). 1,4-Thiazepines **633** ($\text{R} = \text{Et}$, $t\text{-Bu}$, PhCH_2 , $\text{H}_2\text{C}=\text{CHCH}_2$) are the major products of the $\text{Rh}_2(\text{OAc})_4$ -catalyzed reactions of **634** with alcohols. Such reactions involve rearrangement of the oxonium ylide intermediates (80CC798). The CuCl -catalyzed

decomposition of diphenyldiazomethane in the presence of 1,2-dithiane yields 2,2-diphenyl-1,3-dithiepane (89%) as the S—S formal insertion product (85TL5187). 1,3-Dithianes with ethyl diazoacetate give the products of [1,2]-rearrangement of intermediate sulfonium ylides generated by carbenoid capture by a S atom. With **635** (R = Me) the corresponding **636** was produced in 73% yield, and with **635** (R = H) the elimination product **637** is dominant (84JOC1917).

1,4-Dioxocin **620** (16%) was a minor product in a carbene reaction of **618** (R = H) (86JA6062). The reaction of carbenoids from diazo compounds with 2,5-dichlorothiophenes **638** (R = H, Cl) can be utilized for the synthesis of 1,4-oxathiocins **639** (R = H, Cl; R' = CO₂Et, CO₂Bu-*t*, Ts). With the carbenoid from diazodimedone, the intermediate ylide is relatively stable and rearranges to the corresponding **639** at 60–100°C (88CC138). Similarly, substituted 7,8-dihydro-1,4-oxathiocins were recently obtained from the reaction of dibenzoylcarbenoid with 2,3-dihydrothiophene derivatives (95LA187).

The rhodium(II) acetate-catalyzed reaction of ethyl diazoacetate with 1,3-dithiolane **640** (*n* = 1; R = Me), via a [2,3]-sigmatropic rearrange-





ment of the initially generated sulfonium ylide intermediate, gives the corresponding 1,4-dithiocins **641** (**641/642** = 0.58, 92%) (84JOC1917). Similarly, under the same conditions 1,3-dithiane **640** ($n = 2$; $R = \text{H}$) yields both the [2,3]-sigmatropic rearrangement product—the corresponding 1,5-dithiacyclononene **641** ($Z/E = 8.3$)—and the elimination product **642** (**641/642** = 3.4, 97%) (84JOC1917). Heating dithioketals **643** with ethyl diazoacetate or dimethyl diazomalonate and CuSO_4 results in ring expansion via [2,3]-rearrangement of the intermediate sulfonium ylide. The 1,5-dithiacyclononane derivatives **644** (including the betweenane ring system) were obtained in 36–71% yield and E/Z ratio of 5:1–0:1 (85JOC2767).

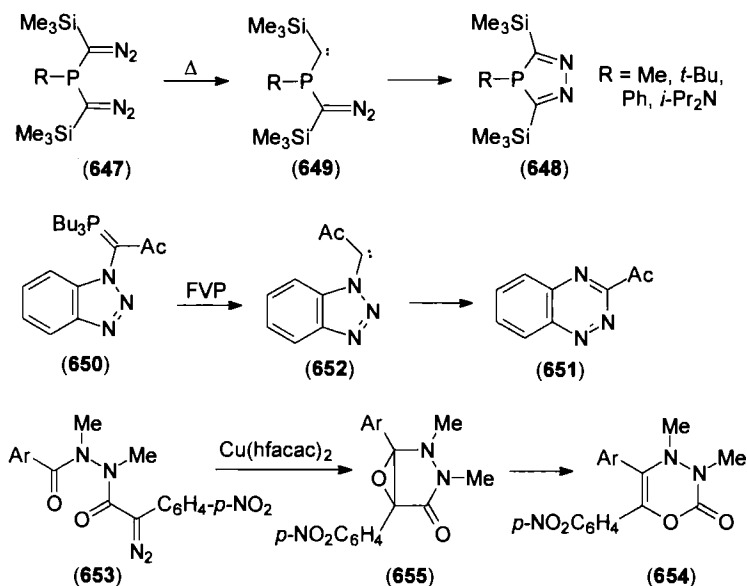
The synthesis of 1,14-dioxacyclohexacosane **645** utilizes the fact that α -diazo ketones undergo $\text{Cu}(\text{acac})_2$ -catalyzed α, α -addition of alcohols, giving α -alkoxy ketones. The second product is crown ether **646** (81CC616).

VIII. Synthesis of Rings with Three or More Heteroatoms

A. HETEROCYCLES WITH TWO NITROGEN AND OTHER HETEROATOMS

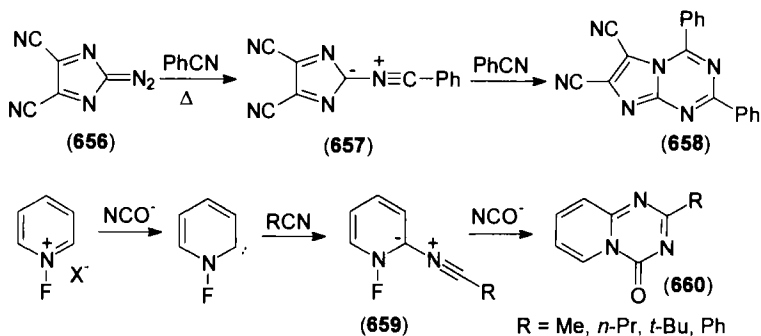
On thermolysis, bis(diazomethyl)phosphanes **647** split off a nitrogen molecule to produce 4*H*-1,2,4-diazaphospholes **648** via the intermediate formation of phosphinocarbenes **649** that undergo [1,5]-ring closure (88TL925).

Flash vacuum pyrolysis of phosphorane **650** results in the extrusion of Bu_3P to give 1,2,4-benzotriazine **651** (26%) and *o*-cyanoacetophenone (16%). The products are apparently derived from the rearrangement of the initially formed carbene **652**, which involves, as in the first example, [1,2]-N migration (93CC1517).



$\text{Cu}(\text{hfacac})_2$ -catalyzed elimination of N_2 from aroyl(α -diazoacyl)hydrazines **653** yields 2H-1,3,4-oxadiazin-2-ones **654** (70%). The reaction occurs consecutively via intramolecular carbonyl ylide formation, 1,3-cyclization into oxirane **655**, and ring opening by the carbon-oxygen bond followed by a $\text{C} \rightarrow \text{O}$ shift with ring expansion (88CB887).

Thermolysis of 2-diazo-4,5-dicyano-2H-imidazole **656** in benzonitrile gives nitrilium ylide **657**, which reacts with a second benzonitrile molecule to afford [4+2]-cycloadduct **658** (79JOC1717). Intermediate formation of nitrile ylide **659** was also supported in a reaction of *N*-fluoropyridinium



SCHEME 31

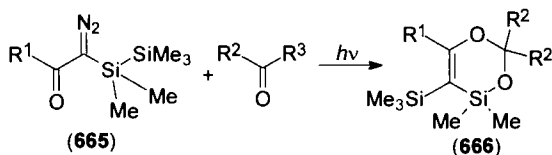
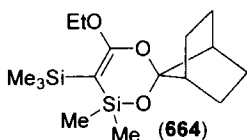
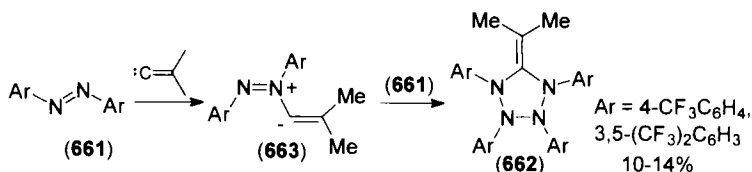
salts with cyanate ion in the presence of nitriles, producing pyrido[1,2-*a*]-1,3,5-triazine derivatives **660** (30–41%) as shown in Scheme 31 (94TL207).

With azobenzenes **661**, vinylidene carbene, generated from silylvinyl triflate, gives tetrazoles **662** as a result of [3+2]-cycloaddition of the intermediate azomethine imines **663** to the N=N bond of a second azobenzene molecule (84JA6015).

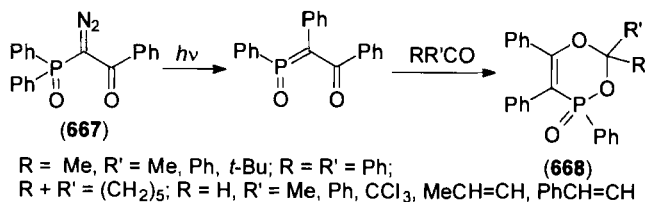
B. HETEROCYCLES WITH TWO OXYGEN AND OTHER HETEROATOMS

Six-membered heterocycles incorporating two oxygen heteroatoms as well as silicon or phosphorus heteroatoms were obtained by [4+2]-cycloaddition of carbonyl compounds with acylsilene or acylphosphene species, which were generated *in situ* from α -diazocarbonyl compounds via a [1,2]-sigmatropic shift in the intermediate ketocarbenes. Thus, 3-silacrylate, produced by thermolysis of diazo(pentamethyldisilanyl)acetic ester, is trapped by 7-norbornanone, giving [4+2]-cycloadduct **664** in 38% yield (83MI2). Photolysis of silyldiazoketones **665** in the presence of nonenolizable carbonyl compounds or ethyl acetate leads to 1,2,4-siladioxenes **666** (91CB1295). With enolizable carbonyl compounds, acylsilenes undergo the ene-type reaction.

Similarly, photolysis of phosphoryldiazoketone **667** generates phosphorylcarbene, which rearranges into benzoylphosphene by a 1,2-phenyl migration. The subsequent [4+2]-cycloaddition of benzoylphosphene to alde-



R¹ = *i*-Pr, R² = Me-CH=CH, R³ = H, 36%; R¹ = R² = Me, R³ = EtO, 28%

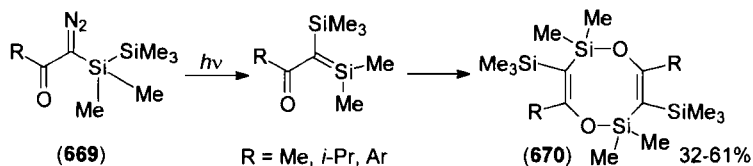


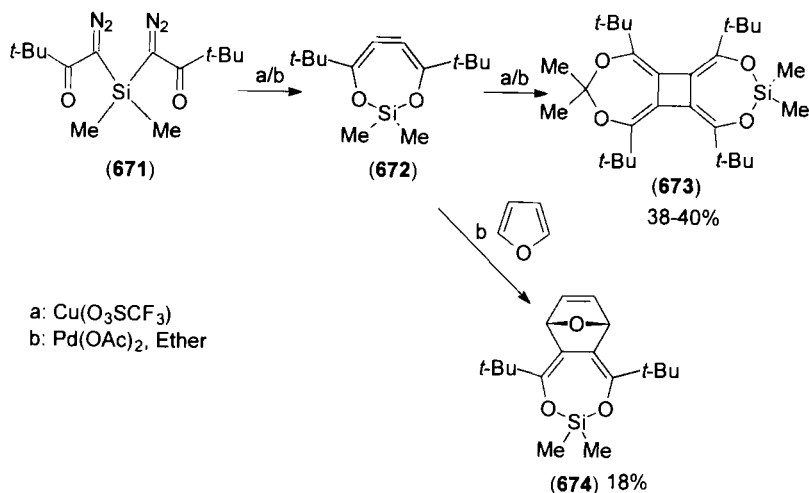
hydres or ketones produces 1,2,4-phosphodioxenes **668** in 23–59% yields (78CB705).

Photolysis of diazo(disilanyl)methylketones **669** in benzene generates acyl(disilanyl)carbenes that rearrange to 3-oxo-1-sila-1-propenes. The latter compounds can either cyclize to 1-oxa-2-sila-3-cyclobutenes or undergo head-to-tail [4+4]-dimerization to form eight-membered heterocycles **670**, depending on the substituent of the acyl function. Cyclodimers are obtained if the substituent at C-3 is not sterically demanding (88CC72; 90CB589).

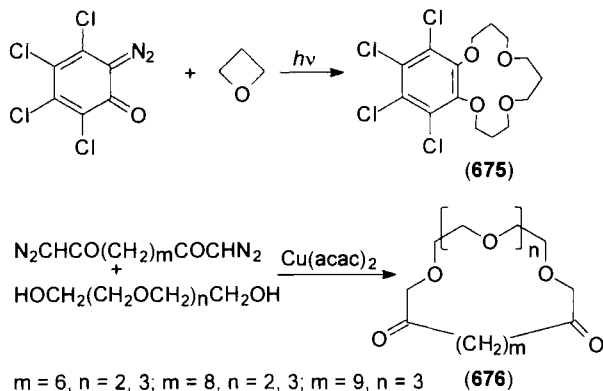
A polycyclic system with a 1,3-dioxo-2-silacyclohepta-4,6-diene fragment was obtained in low yield from bis(diazocarbonyl)silane **671**. In the first stage, a biscarbene or a biscarbenoid, generated in the presence of copper triflate or palladium acetate, forms 1,2-diacylcyclopropene, then rearranging into cyclic cumulene triene **672** by migration of a silicon atom to an oxygen atom. The latter dimerizes to [4]-radialen **673** or reacts with furan to afford **674** (Scheme 32) (89AG1750).

Carbenes, generated by photolysis of di- and tetrachloro-*o*-quinone diazides, react with oxetane in a 1:3 ratio to afford 15-membered crown ethers. Benzocrown ether **675** was obtained in 16% yield (91CB1865). Derivatives of macrocyclic crown ethers with four or five oxygen atoms in a ring were synthesized by Cu(acac)₂-catalyzed cyclization of α,ω -bisdiazoketones with 1, ω -diols or polyethylene glycols. 20–26-Membered crown-4(5) ethers **676** were prepared from the above-mentioned diazo ketones with tri- or tetraethylene glycols in 7–26% yields. Treatment of 1,8-bis(diazoacetyl)octane with dodecane-1,12-diol under the same conditions results in a mixture of 52-membered tetraether **646** (40%) and compound **645** (81CC616).





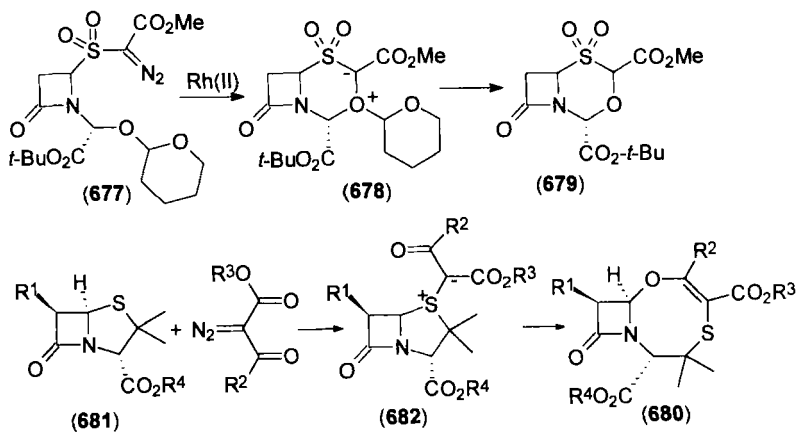
SCHEME 32



C. HETEROCYCLES WITH THREE DIFFERENT HETEROATOMS

Rhodium(II) acetate-catalyzed decomposition of diazo ester **677** gives oxacepham **678** via the formation of oxonium ylide **679** and its subsequent fragmentation (91CC1235).

Eight-membered N,O,S-containing ring systems **680** have become accessible via $\text{Rh}_2(\text{OAc})_4$ -catalyzed decomposition of diazomalonic or diazoacetoacetic esters in the presence of penicillin derivatives **681**. The reaction is mediated by sulfonium ylide **682** and proceeds stereoselectively but in moderate yields. The stereochemical migration control in the ylide occurs

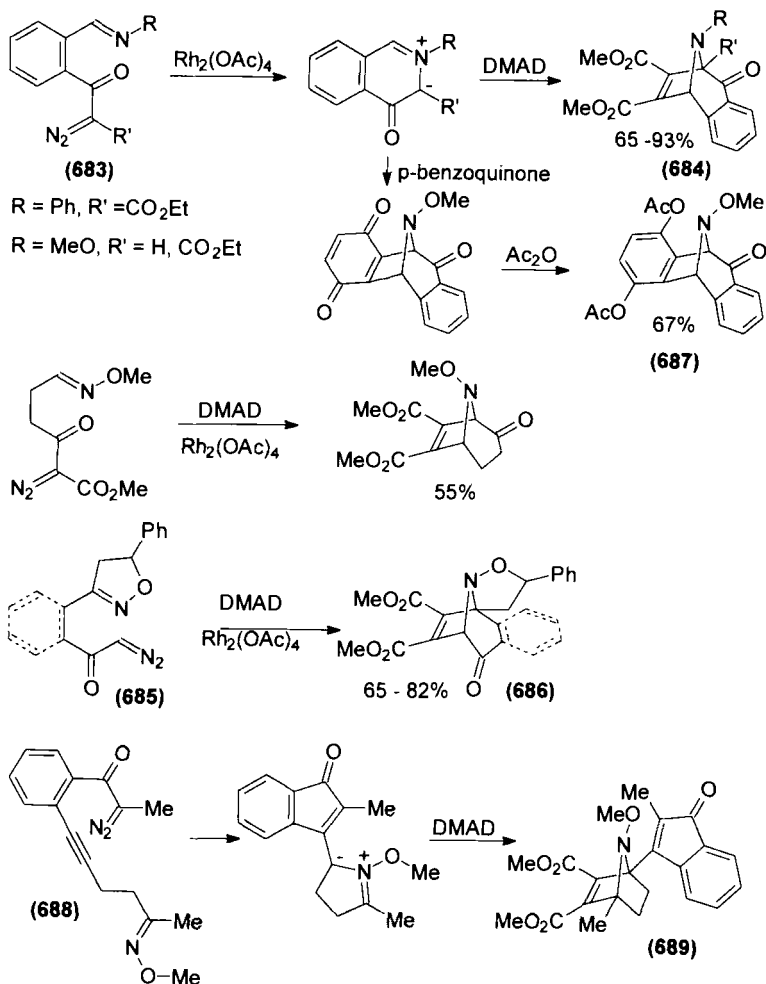


preferentially at the β -face, which is opposite to the C-3 ester and assumed to be the less hindered side (83TL221, 83TL1511; 86JOC624).

IX. Synthesis of Bridged Heterocyclic Systems

A. NITROGEN-BRIDGED COMPOUNDS

The major carbene-based methods for constructing a nitrogen-bridged framework are as follows: tandem cyclization of carbenes with azomethine ylide formation/cycloaddition and tandem cyclopropanation/rearrangement and insertion reactions. The first methodology, introduced by Padwa and co-workers (90JOC405; 94JOC5347), includes cyclization of an α -diazocarbonyl compound containing an imino group in a γ -position with cyclic azomethine ylide formation, followed by 1,3-dipolar cycloaddition to alkenes or alkynes. This method was utilized for the synthesis of 8-azabicyclo[3.2.1]octane derivatives, the yields of which are usually high; however, the outcome strongly depends on the configuration of the imine moiety in the initial diazo compound. A critical point here is that the nitrogen unshared electron pair must be available for interaction with a carbenoid. To illustrate, the $\text{Rh}_2(\text{OAc})_4$ -induced decomposition of *E*-isomer **683** ($\text{R} = \text{MeO}$, $\text{R}' = \text{CO}_2\text{Et}$) in the presence of DMAD furnishes bicyclic compound **684** ($\text{R} = \text{MeO}$, $\text{R}' = \text{CO}_2\text{Et}$) in 93% yield, while the *Z*-isomer gives only an indane derivative (80%), the product of an intramolecular carbenoid C—H insertion (94JOC5347). Isoxazolines **685** with fixed configurations proper for azomethine ylide formation give N-bridged compounds **686** in good yields (90JOC405; 93JOC1144;



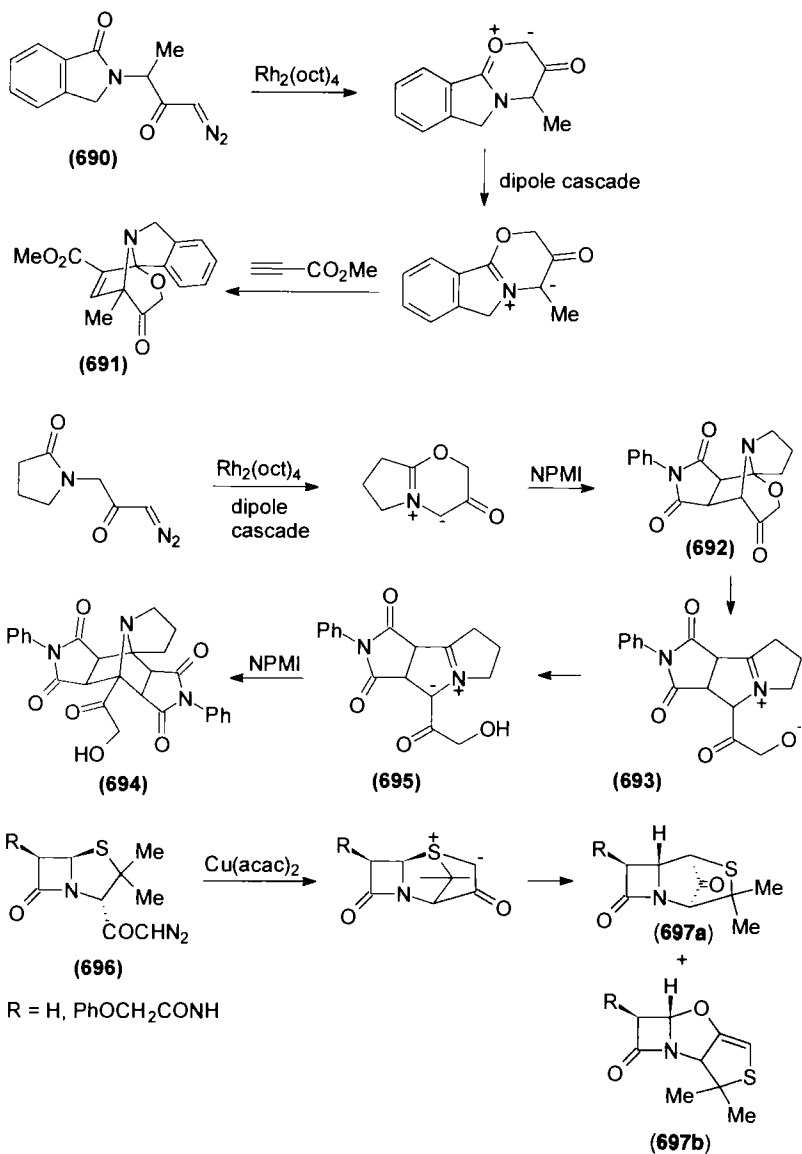
94JOC5347). When *p*-benzoquinone is used as a dipolarophile, the initially formed cycloadducts from **683** ($R = \text{MeO}$, $R' = \text{H}$) can be treated with acetic anhydride to give compound **687**, which contains the basic core dibenzo[*a,d*]cyclohepten-5,10-imine skeleton found in MK-801. However, it should be emphasized that cyclization of the Rh-carbenoids does not occur with weakly basic imines such as pyridines and the aromatic isoxazole system. For the synthesis of a nitrogen-bridged system, Padwa and co-workers have recently reported the successful employment of a domino transformation with displacement of a carbene center, followed by a tandem

cyclization/cycloaddition. $\text{Rh}_2(\text{OAc})_4$ -catalyzed decomposition of diazo oxime **688** in CH_2Cl_2 in the presence of DMAD gave 7-azabicyclo[2.2.1]heptane **689** in 95% yield (95JOC53).

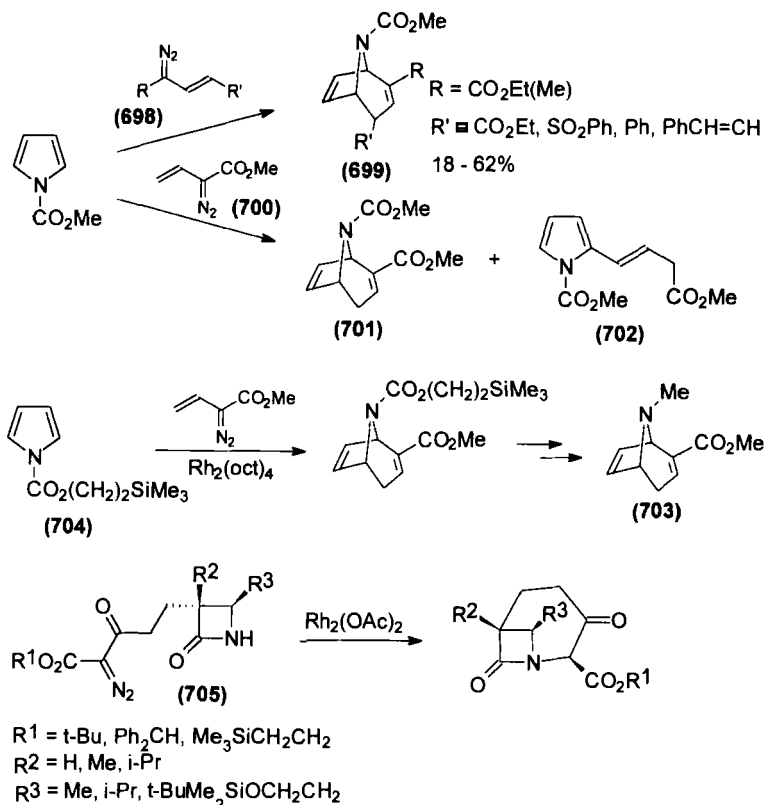
The same research group has proposed an original method for the generation of cyclic azomethine ylide intermediates in the synthesis of N-bridged structures, termed a *dipole cascade* involving a sequential formation of two 1,3-dipoles. It is initiated by Rh(II)-catalyzed diazo ketone cyclization onto a neighboring carbonyl group to generate a carbonyl ylide dipole, which then undergoes a proton shift to give an azomethine ylide (92T7565). This scheme is operative in the Rh(II)-catalyzed decomposition of diazo ketone **690** in the presence of DMAD yielding compound **691**. The primary products of cycloaddition of cyclic azomethine ylide are, however, usually unstable due to the lability of the C—O bond in the C(N)—O fragment of the molecule, decomposing with CH_2O and CO elimination to give pyrrole derivatives and its fused analogs (see Scheme 22). Interestingly, the outcome of the reaction is occasionally dependent on the nature of dipolarophile. Thus, for example, the cleavage of the C—O bond in cycloadduct **692** under the reaction conditions leads to zwitterion **693** with subsequent formation of the 2:1 adduct **694** via intermediate azomethine ylide **695**; but with either DMAD or methyl propiolate as dipolarophiles, this reaction proceeds with CH_2O and CO elimination to the corresponding zwitterions, yielding pyrrole derivatives (92T7565).

The transformation of penicillin-derived diazo ketones **696** into compounds **697a** and **b** with the nitrogen atom in the ring fusion position on treatment by $\text{Cu}(\text{acac})_2$ proceeds via a sulfonium ylide with subsequent rearrangement (77T547; 80TL2451; 82H1647).

The next carbene approach to N-bridged compounds—the reactions of vinyl carbenoids **698** with alkoxycarbonylpyrroles, proceeding as a tandem cyclopropanation/Cope-rearrangement process—provides a direct entry to tropane alkaloids with the 8-azabicyclo[3.2.1]octane skeleton. Vinyl carbenoids containing two electron-withdrawing groups generated by $\text{Rh}_2(\text{OAc})_4$ -catalyzed decomposition of corresponding diazocarbonyl compounds react smoothly with *N*-(methoxycarbonyl)pyrrole to give tropanes **699** as a single product (89TL4653). In the case of vinyl diazocarbonyl agents with a single electron-withdrawing group, as in **700**, the reaction regioselectivity is catalyst-dependent: In passing from rhodium acetate to octanoate the ratio of tropane **701** to alkylation product **702** changes from 55:45 to >90:5 (91JOC5696). The efficacy of this approach to tropane alkaloids has been demonstrated in the synthesis of (\pm)-ferruginine **703** from pyrrole **704** (91JOC5696) and in the enantioselective entry to the tropane system with chiral auxiliaries (92TL6935) using $\text{Rh}_2(\text{oct})_4$ as a catalyst at the key cyclization step.



A successful example of insertion reactions in the synthesis of N-bridged compounds is the $\text{Rh}_2(\text{OAc})_4$ -catalyzed decomposition of β -lactams **705**, which was employed as a key step in the synthesis of several anti-Bredt β -lactams with nitrogen in the bridgehead (86JA6431; 89JA1073).



B. OXYGEN-BRIDGED COMPOUNDS

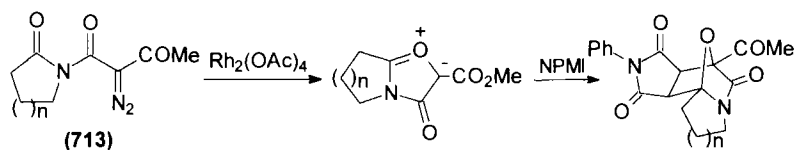
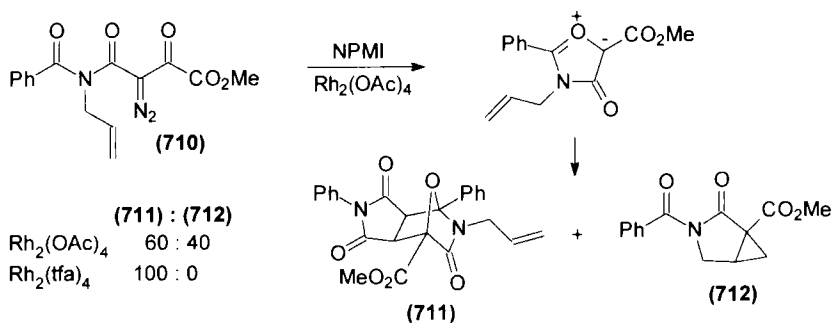
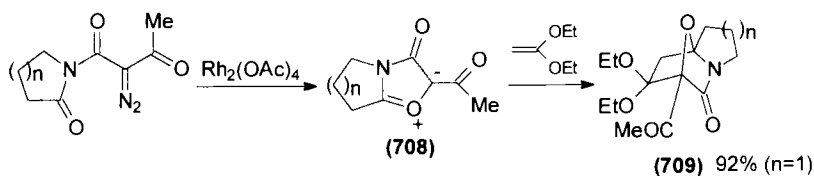
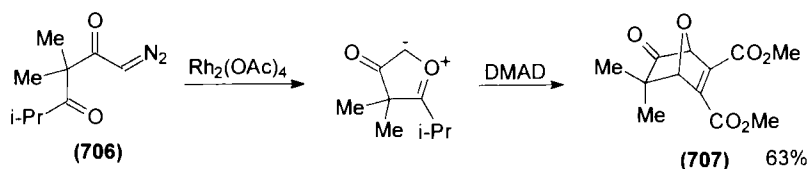
The use of diazocarbonyl compounds in the synthesis of O-bridged systems is the approach of choice. There are a few main synthetic strategies of bridged framework building based on this approach: tandem cyclization with carbonyl ylide formation/cycloaddition, tandem cyclization with oxonium ylide formation/sigmatropic shift, intramolecular cyclopropanation, and cyclization with single bond insertion.

1. Carbonyl Ylide Formation Followed by Intermolecular Cycloaddition

The most effective and well studied method is a tandem methodology including Rh(II)-catalyzed diazo ketone cyclization onto a neighboring carbonyl group to generate a carbonyl ylide with subsequent intermolecular cycloaddition to a multiple bond. Depending on the length of the chain

that links the carbonyl and diazocarbonyl functionalities in the diazo compound—which may be equal to one, two, or three atoms—7-oxabicyclo[2.2.1]heptane, 8-oxabicyclo[3.2.1]octane, and 9-oxabicyclo[4.2.1]nonane derivatives may be obtained.

1-Diazo-2,4-dicarbonyl compounds are used for the preparation of the first type of structures. For example, treatment of diazo diketone **706** with $\text{Rh}_2(\text{OAc})_4$ in the presence of DMAD affords **707** in 63% yield (89TL301). The mild reaction conditions allow a wide variety of 1,3-dicarbonyl moieties to be applied. Thus, the C atom that links the carbonyl groups in compounds like **706** may be incorporated into a small ring or a bridged fragment (89TL301). The former method was used with a cyclopropylidene fragment to construct the skeleton of illudin M and S, which are sesquiterpenes with antitumor activity (94JA2667). Good results were obtained with diazo

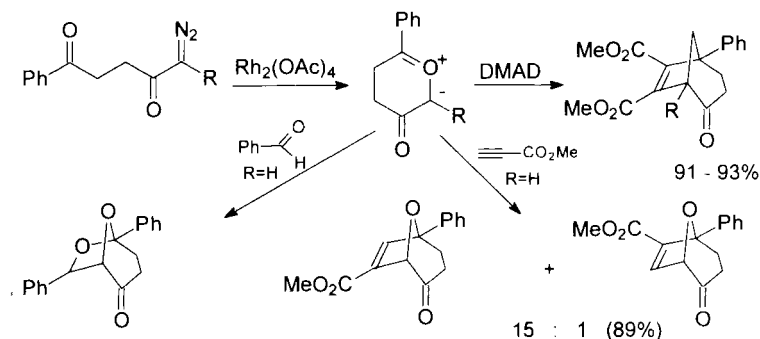


imides, aza analogs of diazo diketones, where the N atom may have aliphatic, aromatic (91JOC820), or olefin (94TL7159) substituents. The catalytic decomposition of these substrates proceeds via the intermediate formation of an isomünchnone dipole (e.g., **708**). The cycloaddition of isomünchnone, derived from diazo amides, to buckminsterfullerene C_{60} has recently been reported to produce 24–52% of cycloadducts (94JOC7949). Rhodium(II)-induced decomposition of diazo compounds with a carbonyl group included in the ring leads to bridged-fused systems as, for example, in the synthesis of tricyclic compound **709** (89TL4077; 91JOC820; 93T2589). 2-Diazo-1,3-dicarbonyl compounds provide a route to structures with acetyl or alkoxycarbonyl substituents in the bridgehead. Here, DMAD, methyl propiolate, methyl propargyl ether, NPMI, diethyl ketene acetal, ethyl cyanofornate, methyl vinyl ketone, and benzaldehyde are possible dipolarophiles. The majority of these reactions usually give high yields of bridged compounds, but a few limitations are known. Thus, intermediate dipoles of the isomünchnone (**708**) type, derived from diazo amides, characteristically undergo [4+2]-reversion with isocyanate fragment elimination. For example, this is the case with reactions with alkynes, which afford furan derivatives (Section IV,C,4). Furthermore, if the diazo compound contains an olefin moiety, intermolecular cyclopropanation is a possible competitive pathway. Thus, treatment of compound **710** with $Rh_2(OAc)_4$ in the presence of NPMI results in a 3:2 mixture of ylide cycloadduct **711** and carbenoid cycloadduct **712** (94TL7159). However, in this case the problem has been solved by the successful choice of catalyst. When the reaction of **710** was carried out with $Rh_2(tfa)_4$, only the target bridged compound was obtained. Such chemoselectivity was explained by the differences in electrophilicity between the various Rh(II)-carbenoid intermediates, implying involvement of the metal and its ligand during the formation of the isomünchnone dipole. The reactions of cyclic carbonyl ylides may proceed both stereospecifically (89TL301) and with a mixture of isomer formation (91JOC820; 93T2589). Padwa *et al.* (89TL4077) reported that the $Rh_2(OAc)_4$ -catalyzed decomposition of **713** in the presence of NPMI shows little *exo/endo* selectivity when $n = 1$ or 3 and results in a single stereoisomer when $n = 0$ or 2.

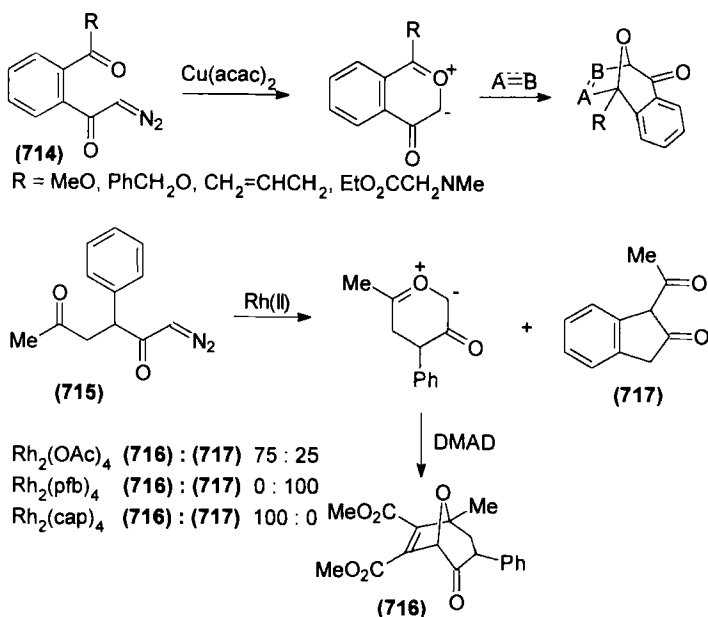
Intermolecular cycloaddition of cyclic carbonyl ylides derived from diazo ketones, diazo diketones, diazo ketoesters, and their aza and oxa analogs containing 1,4-dicarbonyl fragments leads to the formation of 8-oxabicyclo[3.2.1]octane derivatives, which are useful intermediates in the synthesis of various natural compounds (85TL3899; 89TL1491; 90JA3100; 94JOC6965). The synthetic availability of initial 1-diazo-2,5-dicarbonyl compounds, together with the mild neutral conditions for ylide generation, allows a very wide range of changes in the structure of both the

substrate and the dipolarophile. This peculiarity explains why a wide variety of compounds with the 8-oxabicyclo[3.2.1]octane skeleton have become accessible in the last few years. Several aspects of these syntheses are notable. First, the reactions of substrates with a 1-diazo-2,5-pentanedione backbone are very clean and generally proceed in high yields, especially with activated dipolarophiles (88JOC2875; 89TL1491; 90JA3100; 92JA1874), demonstrating the high regioselectivity with unsymmetric dipolarophiles (89CC921) (Scheme 33). Good results have been obtained in the synthesis of 8-oxabicyclo[3.2.1]octane derivatives with O,N and O,O heteroatoms in the bridged framework by the Rh(II)-catalyzed decomposition of diazo compounds containing N (92T7565) or O atoms (89CC921, 89TL4077; 93JOC4646) in the chain that links the diazocarbonyl and carbonyl functionalities. By using the tandem cyclization/intermolecular cycloaddition protocol, the tricyclic bridged-fused frameworks also may be constructed from diazo compounds whose 1,4-dicarbonyl backbone is partly included in the cyclic fragment. This methodology has been successfully applied to structures in which the 8-oxabicyclo[3.2.1]octane framework is fused to cyclopentane (90JA3100), fluorene (86BCJ255), isobenzofuran (87TL5407; 88JA2894), and pyrrolidine (89JA6451, 89TL4077; 92JA593, 92T7565) rings. The cycloaddition of 1-alkoxy-2-benzopyrylium-4-olates, derived from *o*-alkoxycarbonyl- α -diazoacetophenones **714**, to alkenes (81BCJ240; 84BCJ926; 85BCJ2212), alkynes (79BCJ3582; 88JA2894), isocyanates (86CC1266), and carbonyl compounds (83CL1453; 85BCJ1787; 86BCJ2489) has received the most study. The reactions with the corresponding amides occur in a similar way (89JA6451; 90JA2037).

Aliphatic and aromatic C—H insertion is often competitive with ylide formation. Generally, the C—H insertion with five-membered ring formation is most characteristic of carbenoids possessing a relatively low electro-



SCHEME 33

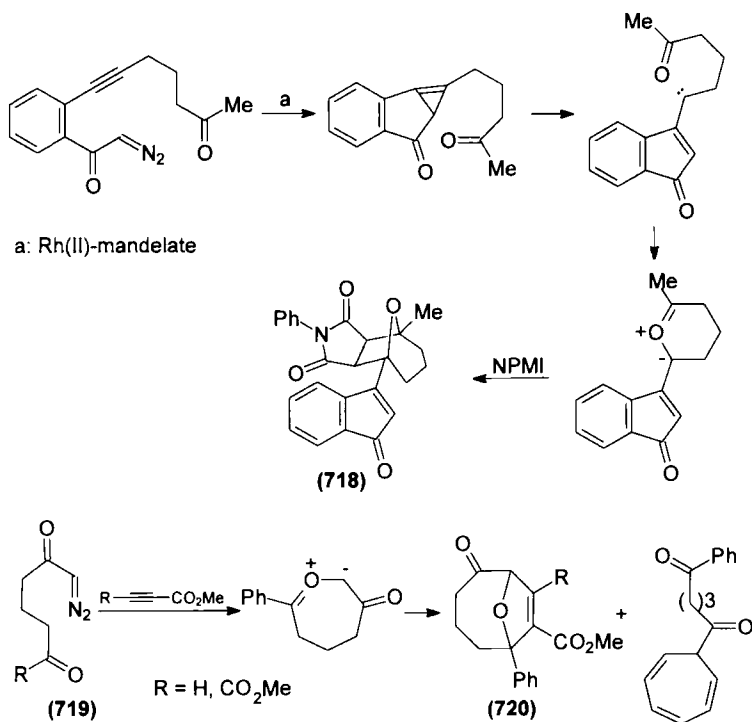


SCHEME 34

philicity; such carbenoids are usually derived from diazo ketones and diazo esters. When there is no C—H bond suitable for insertion, cyclopropanation of benzene, commonly used as the solvent, can be realized. Furthermore, Padwa and co-workers have found that chemoselectivity in these competitive transformations depends on the inherent electron demand from the ligand of the Rh(II)–carbene intermediate. Scheme 34 illustrates the obvious ligand-dependent selectivity of the Rh(II)-catalyzed decomposition of diazo ketone **715** in the presence of DMAD (92JA1874).

Padwa and co-workers (89TL2633; 93JA2637) have elaborated an elegant modification of the cyclization/cycloaddition approach that involves the displacement of a carbene center and provides access to O-bridged compounds with an indenone moiety. An illustrative example is the synthesis of compound **718** through the Rh(II)-catalyzed decomposition of α -diazo ketones bearing tethered alkyne units in the presence of a dipolarophile (91JOC2523).

The tandem cyclization/intermolecular cycloaddition procedure is also feasible for the synthesis of 9-oxabicyclo[4.2.1]nonane derivatives via the generation of seven-membered cyclic carbonyl ylides. The $\text{Rh}_2(\text{OAc})_4$ -catalyzed decomposition of **719** in the presence of DMAD or methyl propiolate in benzene gives **720** together with the product of a formal carbenoid



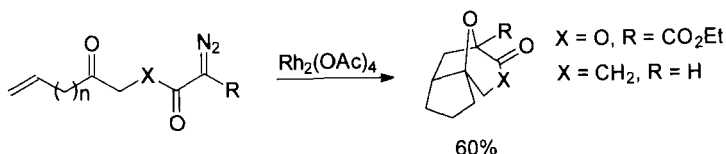
insertion into benzene (3 : 1). This result implies that an additional methylene group in the chain linking the diazoketo and carbonyl groups sufficiently decelerates the intramolecular cyclization (89TL301).

2. Carbonyl Ylide Formation Followed by Intramolecular Cycloaddition

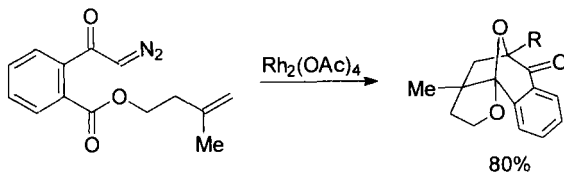
The next efficient and graceful tandem cyclization/cycloaddition approach to O-bridged compounds is the intramolecular cycloaddition of cyclic carbonyl ylides to C=C bonds. The structural diversity of bridged molecules accessible via this route is defined by the size of the diazodicarbonyl moiety cyclizing into an ylide and that of the olefin tether, and also by the position of the latter with respect to the diazodicarbonyl backbone. Thus, the Rh(II)-catalyzed decomposition of diazo compounds with an olefinic chain at the "carbonyl" side of the molecule furnishes tricyclic bridged-fused compounds. Some successful examples of the synthesis of 8-oxabicyclo[3.2.1]octane systems fused to cycloalkane (88TL1677, 88TL6009; 89CC921; 93JOC4646), indane (88JOC2875), benzene, and tetrahydrofu-

ran (88JA2894) rings are shown in Schemes 35–38. Similarly, 2-aza-7-oxabicyclo[2.2.1]heptane systems can be obtained in high yields from acyclic and cyclic diazo imides **721** with the pendant olefin moiety. Here, $\text{Rh}_2(\text{pfb})_4$ seems to be the catalyst of choice, allowing the reactions to be carried out at room temperature in CH_2Cl_2 (94JOC1418). Notably, all these reactions are completely diastereospecific. This stereochemical outcome is the consequence of an *endo*-cycloaddition of the neighboring π -bond across the transient carbonyl ylide dipole.

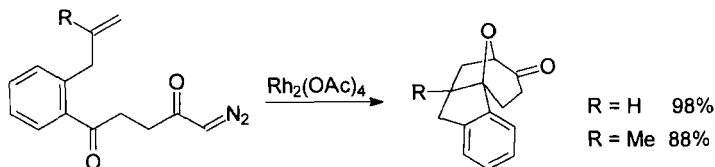
Unique synthetic opportunities, particularly in alkaloid chemistry, are opened up on applying this protocol to diazo imides bearing a tethered heterocyclic ring. Thus, isomünchnone dipole, which is derived from these compounds, undergoes intramolecular cycloaddition across the heterocyclic π -bond to produce bridged polyfused systems. Some examples of reactions with 2-furyl- and 1-indolyl-substituted substrates are shown in Schemes



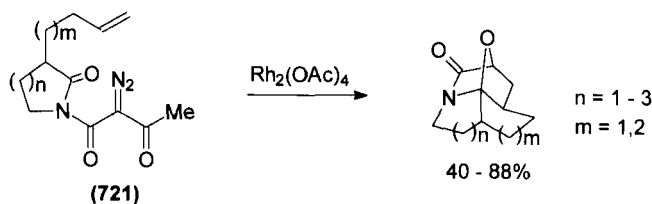
SCHEME 35



SCHEME 36



SCHEME 37



SCHEME 38

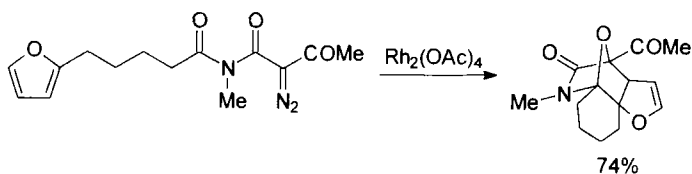
39 and 40. Although efforts to obtain the corresponding S-analogs from thiophene-containing diazo compounds have failed, the cycloaddition of NPMI to a transient carbonyl ylide takes place (94JOC7072).

Recently, Dauben *et al.* used the tandem cyclization/intramolecular cycloaddition approach as a key step of the formation of the B- and C-rings of the diterpenoid tiglaine skeleton, obtaining **722** in 86% yield (93JOC7635). In addition, Padwa and co-workers have reported the effective application of this approach in the synthesis of tricyclic nitrogen compounds, B-ring homologs of erythrinane alkaloids (94JOC5518).

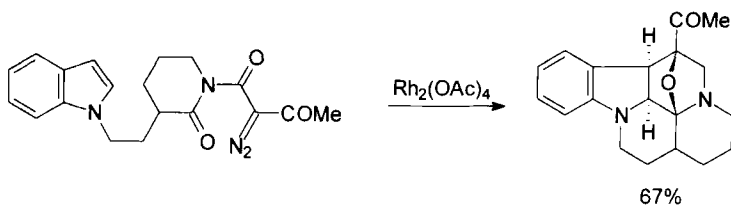
The attempted synthesis of O-bridged compounds from mixed allyl esters of diazomalonic acid of the type **723**, in which the olefinic chain is located at the "diazo" side of the molecule, has failed (93JOC4646). However, tethering the olefin moiety to the chain that links the carbonyl and diazocarbonyl functionalities provides a great variety of tricyclic-nonfused compounds (82T1477; 92JA1874; 94TL7159). The most representative examples are shown in Schemes 41 and 42.

The intramolecular version of the above-mentioned domino transformation with carbene-center displacement has been explored by Padwa and co-workers in an effective route to bridged tricyclic compound **724** (95JOC53). The synthesis of compound **725** illustrates the feasibility of utilizing the cyclization/intramolecular cycloaddition sequence in combination with, for example, intramolecular cyclopropanation or other similar procedures (82T1477).

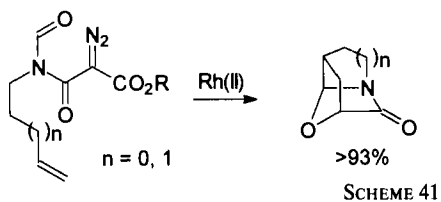
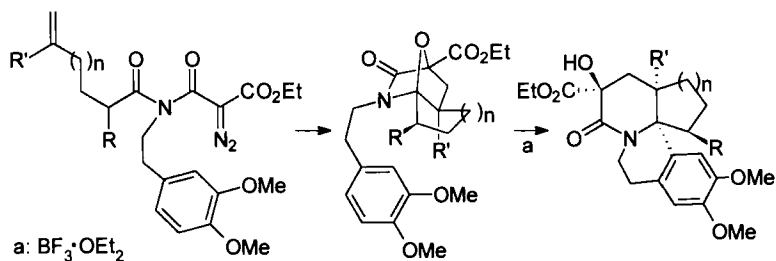
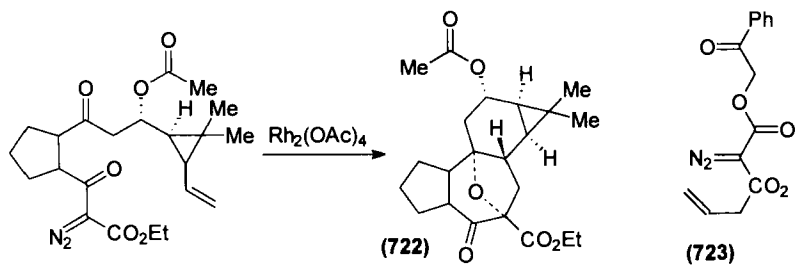
Although virtually of no synthetic significance, the dimerization of carbonyl ylides is capable of providing O-bridged compounds. It is noteworthy that both "head-to-tail" **726** (88TL317) and "head-to-head" **727** (86BCJ255) dimerization modes can be in effect here.



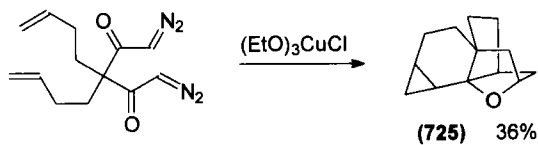
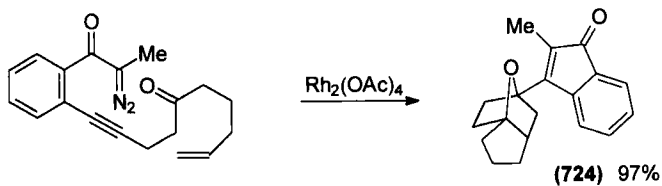
SCHEME 39



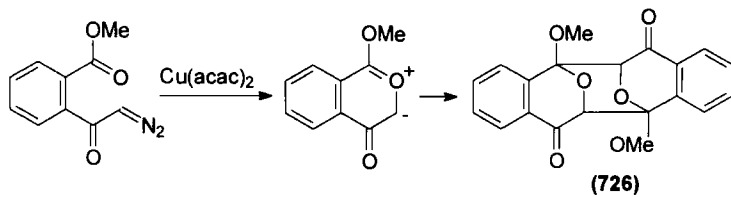
SCHEME 40

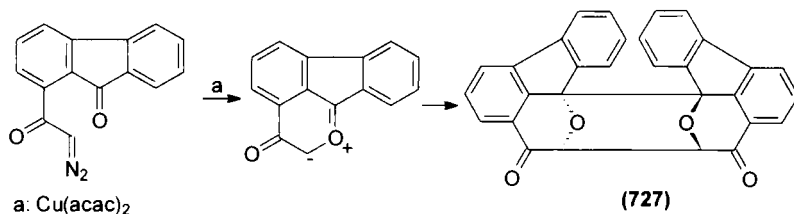


SCHEME 41



SCHEME 42

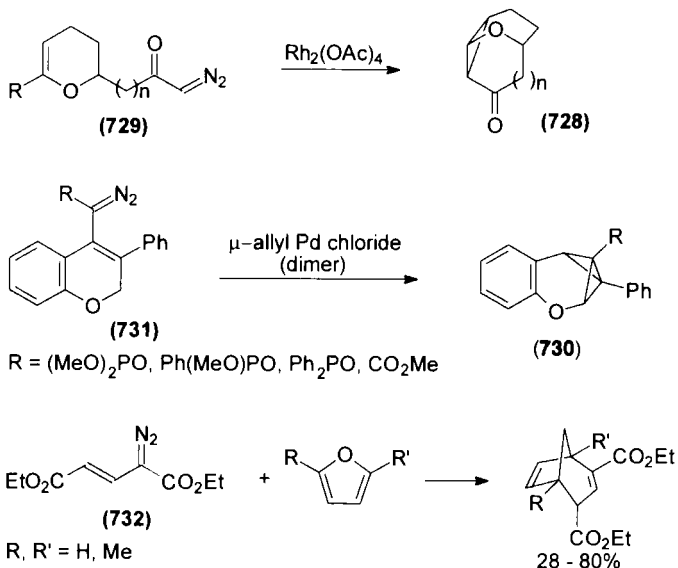




3. Intramolecular Cyclopropanation

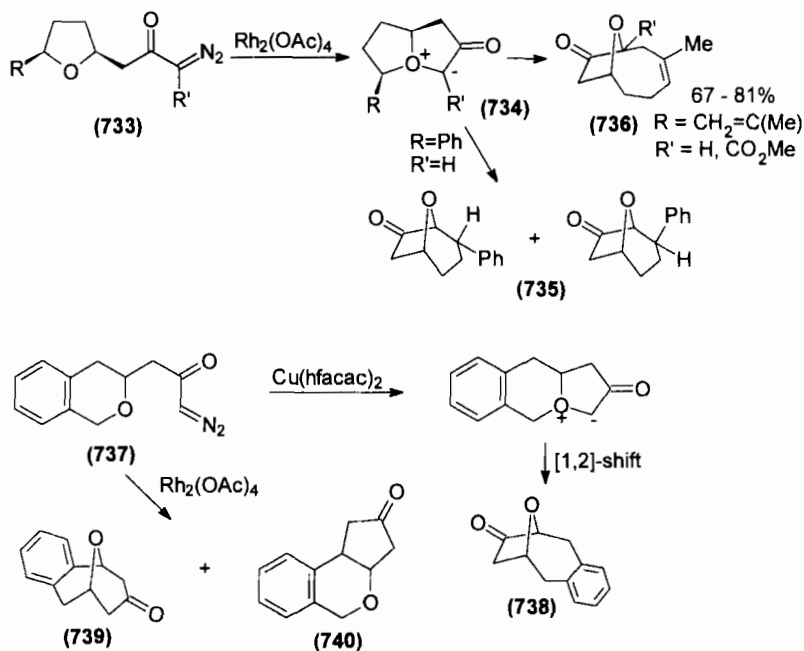
Intramolecular cyclopropanation in oxygen-containing compounds may also be of synthetic utility for the preparation of O-bridged structures. Adams *et al.* have described the synthesis of **728** from 2-substituted 3,4-dihydropyrans **729** (87JA5432; 91JOC4494) and showed that when $n = 0-3$ the transannular cyclopropanation proceeds in high yields. However, when $n > 3$ or $n = 2$, substrates lacking a substituent R give exclusively C—H insertion products. Regitz and co-workers have successfully obtained compounds **730** containing a bicyclo[1.1.0]butane fragment in the heterocyclic system from **731** (87CB1397).

Interaction of furans with vinylcarbenes, derived from diazo acetates **732**, presumably proceeds via cyclopropanation of the furan double bond



followed by a Cope rearrangement, the yields being strongly dependent on the furan ring substitution (85TL5659; 87T4265).

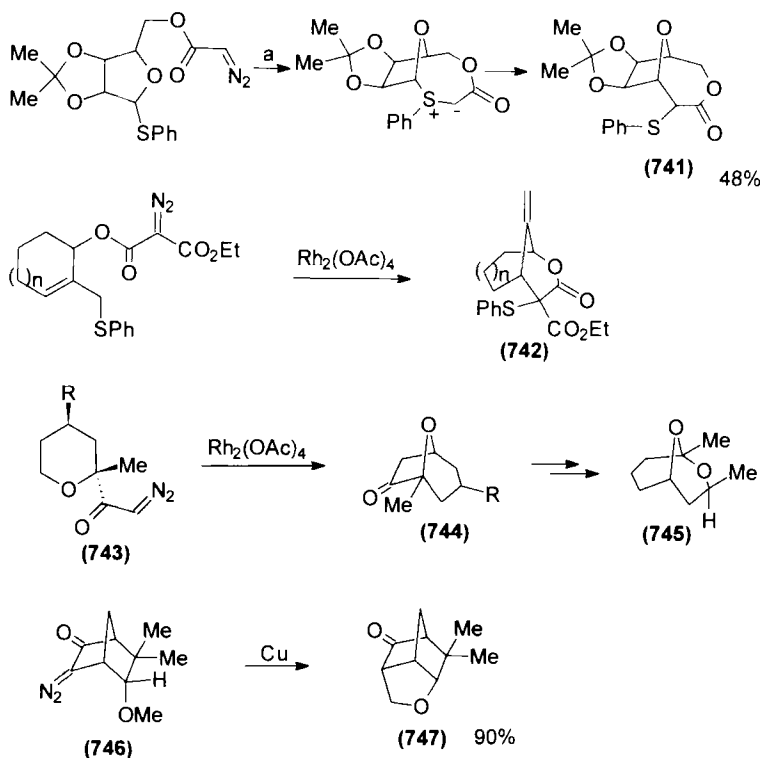
Examples of the syntheses of O-bridged compounds via oxonium ylides are not as numerous as those via a carbonyl ylide. The Rh(II)-induced decomposition of 2-tetrahydrofuryldiazoacetates **733** offers some interesting synthetic feasibilities. The carbenoid formed under these conditions cyclizes onto an O atom of the heterocycle to produce oxonium ylide **734**, which is further stabilized by the nature of the substituent at the C₅ position of the ring. With phenyl-substituted derivatives, a [1,2]-sigmatropic shift in a transient ylide takes place, yielding a diastomeric mixture of 8-oxabicyclo[3.2.1]octanes **735** [93JCS(P1)2857]; and with isopropenyl-substituted tetrahydrofurans, a [2,3]-sigmatropic shift in the transient ylide occurs to give **736** (86JA6060). The nature of the catalyst may also markedly influence the product distribution. Thus, decomposition of diazo ketone **737** in the presence of Cu(hfacac)₂ occurs via oxonium ylide formation followed by a [1,2]-shift to produce 9-oxabicyclo[4.2.1]nonane derivative **738** in almost quantitative yield. But with Rh₂(OAc)₄, only the C–H insertion products **739** and **740** are formed (94JOC6892).



4. Miscellaneous Reactions

The sequence including intramolecular sulfonium ylide formation from the reaction of a Rh(II) carbenoid with a divalent S atom and the rearrangement of the ylide was employed in the preparation of lactones **741** (93TL7627) and **742** (91TL6159).

The C—H insertion reactions of carbenes and carbenoids, while not infrequently providing undesirable products, may offer a route to O-bridged compounds. Transannular cyclization via insertion of carbenoids derived from **743** furnishes 8-oxabicyclo[3.2.1]octane **744** in high yields (92TL1143). Unsubstituted compound **744** (R = H) is a key intermediate in the synthesis of pheromone **745**, which has been isolated from Norwegian spruce trees (87TL4773). In diazo norbornanone **746**, where intramolecular ylide formation is impossible, insertion into the C—H bond activated by the neighboring oxygen takes place to afford the tricyclic compound **747** in high yield (79CJC1668).



X. Conclusion

It is clear from the publications surveyed here that carbene and carbenoid reactions have enormous potential in heterocyclic synthesis. This is due not only to the outstanding possibilities for constructing complex ring systems via catalytic reactions of diazo compounds and producing useful heterocyclic building blocks via accessible carbenes, but to great achievements in stereoselective carbene synthesis, as well. Certainly, many applications of the carbene approach to heterocycles remain undiscovered; thus, one can assume that important findings will be forthcoming.

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75ACR209
75H193
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Thienopyrimidines: Synthesis, Reactions, and Biological Activity

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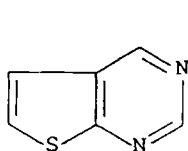
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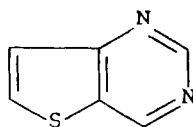
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I. Introduction

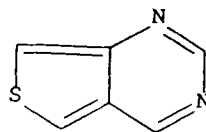
There are three isomeric thienopyrimidines: thieno[2,3-*d*]pyrimidines **1**, thieno[3,2-*d*]pyrimidines **2**, and thieno[3,4-*d*]pyrimidines **3**. The present review deals with these three systems and their chemically and biologically active derivatives. However, it will not cover any additional condensed systems owing to the large number of references in this area.



1



2



3

II. Structure

A. STABILITY OF THE PARENT RING SYSTEMS

Although the parent isomers **1** and **2** have been synthesized by more than one procedure, attempts to prepare the parent isomer **3** have been unsuccessful. Isomer **1** was first prepared by catalytic reduction of the 4-chloro or 4-bromo derivatives or by oxidation of the 4-hydrazino derivative [68CR(C)128; 76BSF761], and **2** was similarly obtained from the 4-chloro or 4-hydrazino derivatives [67CR(C)100; 68CR(C)1706; 71T487]. The failure to obtain **3** was attributed (74BSF1629) to the instability of this isomer. This isomer has only one nonionic mesomeric form, unlike compounds **1** and **2**, which have two nonionic mesomeric forms and are therefore stabilized by greater resonance energy.

B. MOLECULAR SPECTRA

¹H NMR: The proton chemical shifts of thieno[2,3-*d*]pyrimidine **1** and long-range coupling of H2,H6 are useful in assigning the position of its substituents (75JHC525; 77BSF676; 80JHC1019). The effects of 4-aryl substituents on the thiophene proton chemical shifts and a long-range ⁷J_{H6-F} coupling of 4-(*o*-fluorophenyl) derivatives have been studied (75BCJ147, 75BCJ974, 75BCJ3373; 76BCJ1395). Similarly, ¹H NMR spectra of thieno[3,2-*d*]pyrimidines and the effects of 4-substituents on the other ring proton signals and the long-range H4,H7 coupling have been reported (71T487; 77BSF676).

UV: The UV spectra of the 2,4-diamino derivative of **1** and its pK_a value were measured (69JOC821). The UV spectra of the 4-oxo derivatives of **1** and **2** are known (68MI1).

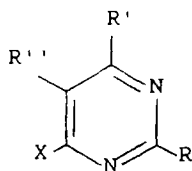
Mass spectra: The mass spectra and fragmentation pattern of thieno[2,3-*d*]pyrimidine-2,4-diones (85JHC889) and thieno[3,4-*d*]pyrimidine-2,4-diones have been reported (91MI3).

III. Synthetic Approaches to Thieno[2,3-*d*]pyrimidines

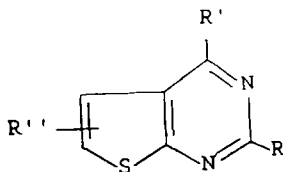
A. FROM PYRIMIDINE DERIVATIVES

1. Condensation with Thiophene and Its Alkyl or Aryl Derivatives

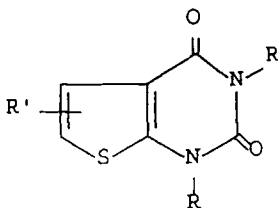
Bromination of 4-mercapto-5-allyl-2,6-dimethylpyrimidine **4** (X = SH, R = R' = Me, R'' = allyl) followed by dehydrobromination of the inter-



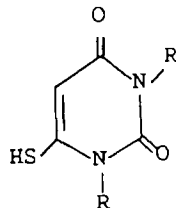
4



5



6



7

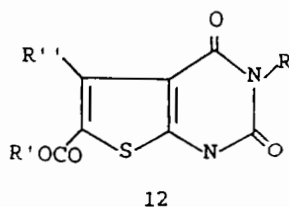
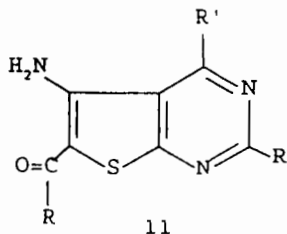
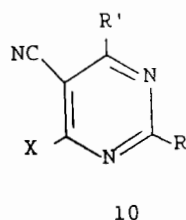
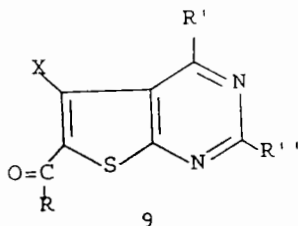
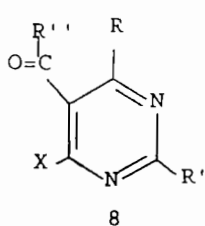
mediate dihydro derivative gave 2,4,6-trimethylthieno[2,3-*d*]pyrimidine **5** (82KGS118).

Compounds of type **5** were also obtained by the action of NaSH on **4** ($X = \text{Cl}$, $R'' = \text{C}\equiv\text{C}-\text{Ph}$ or $\text{C}\equiv\text{C}-\text{SiMe}_3$) (82CPB2417; 86CPB2719) or by the action of P_2S_5 on **4** ($X = \text{OH}$, $R'' = \text{C}\equiv\text{C}-\text{Ph}$) (82CPB2417). Compounds **4** ($X = \text{OH}$, $R'' = \text{CH}_2\text{COCH}_3$) underwent thiation and cyclization to give derivatives of **5** (69BSF4344).

Condensation of **4** ($R'' = \text{H}$, $X = \text{SH}$) with α -halocarbonyl compounds gave **5** (69JMC227, 69USP3470183; 80JOC3651). Similarly, thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **6** were obtained from the uracil derivatives **7** (72CPB404; 90JHC717).

2. Condensation with Thiophenecarboxylates and Carbonyl Derivatives

Cyclocondensation of 4-chloro-5-acylpyrimidines **8** ($X = \text{Cl}$, $R'' = \text{alkoxy}$) with thioglycolic acid derivatives afforded the 5-hydroxy-6-carboxylic acid derivatives **9** ($X = \text{OH}$, $R = \text{OMe}$ or NHAr) (71JHC445; 72USP3654204; 83URP725433). The methylsulfonylpyrimidines **8** ($X = \text{SO}_2\text{Me}$) reacted similarly with methyl thioglycolate and triethylamine to give **9** (88JHC959). The 5-cyano derivatives **10** ($X = \text{Cl}$) also reacted with thioglycolates to give the 5-amino-6-carboxylates **11** ($R'' = \text{OR}$) (71JHC445; 77JHC361; 88JHC959, 88KGS1559, 88LA633; 89JPR893, 89JPR957). The 4,5-diamino derivative **11** ($R' = \text{NH}_2$) was prepared by the condensation of **10** ($R = \text{Ph}$, $R' = \text{NH}_2$, $X = \text{Cl}$) with diethyl α -mercaptosuccinate (77JHC361).



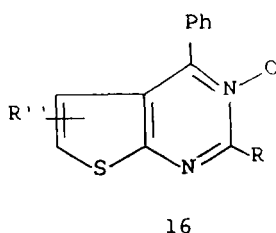
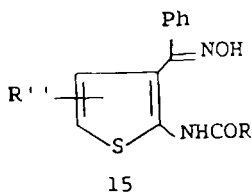
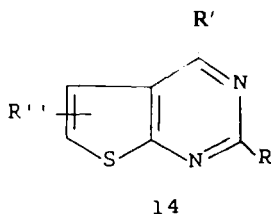
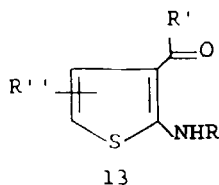
Similar condensation reactions with the appropriate uracil derivatives yielded the dioxo derivatives **12** ($R' = \text{H}, \text{NH}_2$) (90JHC717).

Cyclocondensation of 4-mercapto-5-acylpyrimidines **8** ($X = \text{SH}$) and the 5-alkoxycarbonyl derivatives **8** ($X = \text{SH}, R' = \text{OR}$) with α -halocarbonyl compounds or α -halo esters gave the corresponding 6-carbonyl derivatives **9** ($X, R = \text{alkyl or aryl}$) or their 5-hydroxy derivatives **9** ($X = \text{OH}, R = \text{alkyl or aryl}$) or the carboxylate **9** ($X = \text{OH}, R = \text{alkoxy or NHR}$) (73LA1025; 88JIC695, 88PHA537; 89MI3, 89MI4, 89MI5, 89PHA348, 89PHA492; 90JIC327, 90MI3, 90MI5, 90PHA216; 92MI1). Similarly, the 4-mercapto-5-cyanopyrimidines **10** ($X = \text{SH}$) reacted with active α -halomethylene compounds to give the corresponding 5-amino-6-carbonyl derivatives **11** or their 6-carboxylic acid derivatives **11** ($R = \text{alkoxy}$) [71IJC761; 75JAP(K) 75/140487; 79EGP136500; 83S402; 84JCS(P1)2447; 87KGS1377; 88MI2; 89MI2; 90PHA216; 91PS223].

B. FROM THIOPHENE DERIVATIVES

1. Condensation with Pyrimidine and Its Alkyl and Aryl Derivatives

Cyclization of 2-amino-3-acylthiophenes **13** ($R' = \text{H}$) with formamide gave the corresponding substituted thienopyrimidines **14** (76BSF761). Condensation of 2-acylamino-3-acylthiophenes **13** ($R' = \text{COR}$) with ammonia (78MI1), ammonium acetate in acetic acid (72URP355167; 74KGS58), or



in DMSO [73GEP(O)2310016] afforded the corresponding derivatives **14**. Also, heating **13** ($R = \text{COCH}_2\text{CH}_2\text{CN}$) in ethanolic NaOH gave **14** ($R = \text{CH}_2\text{CH}_2\text{COOH}$) (76JAP76/43796).

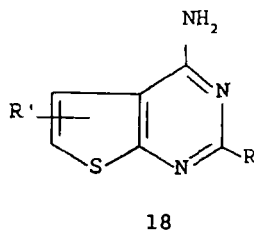
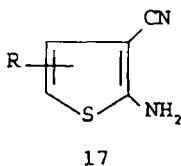
Condensation of **13** ($R = \text{COCH}_2\text{I}$) with KSCN in ethanol produced **14** ($R = \text{SCH}_2\text{COOEt}$) [77JAP(K)77/46095].

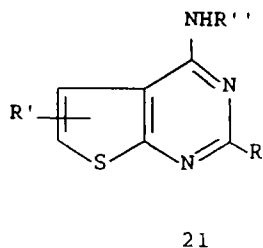
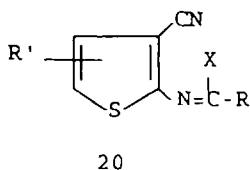
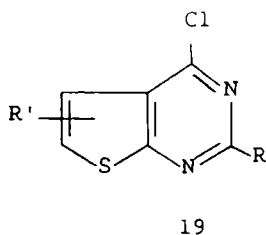
Cyclization of oximes **15** with HCl gave the *N*-oxides **16**, which were reduced with PCl_3 to give the corresponding **14** (74MI1; 75JPR705).

2. Condensation with 4-Aminopyrimidines

2-Amino-3-cyanothiophenes **17** with formamide gave the corresponding 4-aminothienopyrimidines **18** ($R = \text{H}$) [70JPS1348; 74KGS196; 76IJC(B)537; 83MI1; 88JPR585; 89MI1; 90IJC(B)1070].

Condensation of nitriles (RCN) with **17** in a basic medium afforded the corresponding **18** [89ZN(B)488; 92AP301, 92PS93]. However, treatment of **17** with nitriles in the presence of dry HCl gave the 4-amino derivatives **18**, the 4-chloro derivatives **19**, or a mixture of both depending on the nature of the R group of the nitrile (80JHC1497; 83TL4611; 85JHC825; 90JHC119).



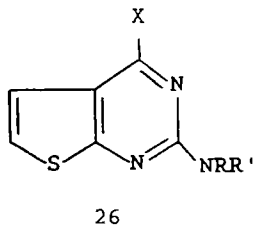
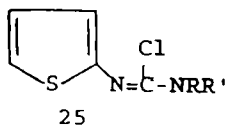
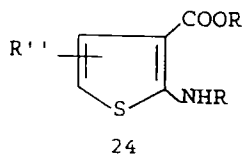
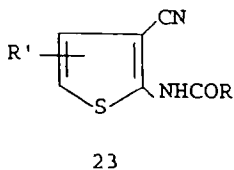
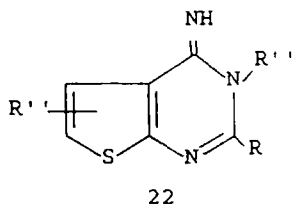


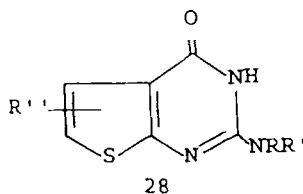
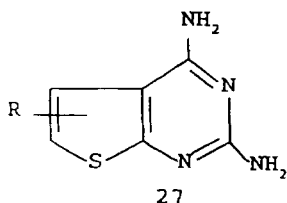
Heating 3-cyano-2-(ethoxymethylene)aminothiophenes **20** ($X = \text{OEt}$) with amines ($R''\text{NH}_2$) gave the corresponding 4-substituted amino derivatives **21** ($R = \text{H}$) (84EUP103114). Condensation of **20** ($X = \text{OEt}$) with ammonia afforded the formamidines **20** ($X = \text{NH}_2$), which were cyclized with NaOMe to **18** ($R = \text{H}$) [66AG(E)131; 67JOC2376].

Condensation of **20** ($R = \text{Me}$, $X = \text{OEt}$) with hydrazine gave the corresponding 3-amino-4-imino derivative **22** ($R'' = \text{NH}_2$) (81JHC43).

2-Acylamino-3-cyanothiophenes **23** with aromatic amines in the presence of P_2O_5 and N,N -dicyclohexylamine gave the corresponding 4-aryl amino derivatives **21** ($R'' = \text{Aryl}$) via imino intermediates **22** ($R'' = \text{aryl}$), which could be isolated (81CS245; 88CS195). Similar treatment of 2-acylaminothiophenecarboxylates **24** also gave derivatives of **21** (81CS135).

Reaction of N -(2-thienyl)chloroformamidines **25** with N -cyanomorpholine gave the corresponding N,N -disubstituted amino derivatives **26** ($X = \text{morpholino}$). Other derivatives of **26** ($X = \text{OH}$, SH , SeH , $\text{N}=\text{CMe}_2$) were similarly prepared (80LA699).





3. Condensation with 2,4-Diaminopyrimidines

Condensation of **17** with guanidine or chloroformamidine-HCl gave the corresponding 2,4-diaminothiopyrimidines **27** [73JMC185, 73JMC188, 73JMC191; 89MI1; 90HCA797, 90IJC(B)1070; 92PS93].

4. Condensation with Amino-Oxopyrimidines

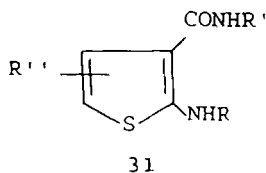
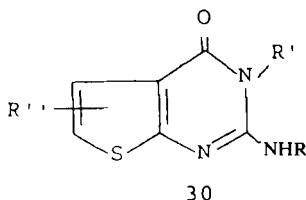
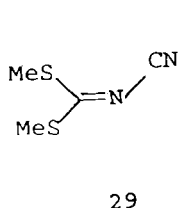
Condensation of **25** with cyanates formed the corresponding 2-disubstituted amino-4-oxo derivatives **28** (80LA699). 2-Aminothiophene-3-carboxylates **24** with *N*-cyanoamides [83IJC(B)76; 84JHC375], methoxyamidines, or methylthioamidines [75GEP(O)2411273, 75GEP(O)2411274] gave the corresponding 2-aminothiopyrimidin-4(3*H*)-ones **28**.

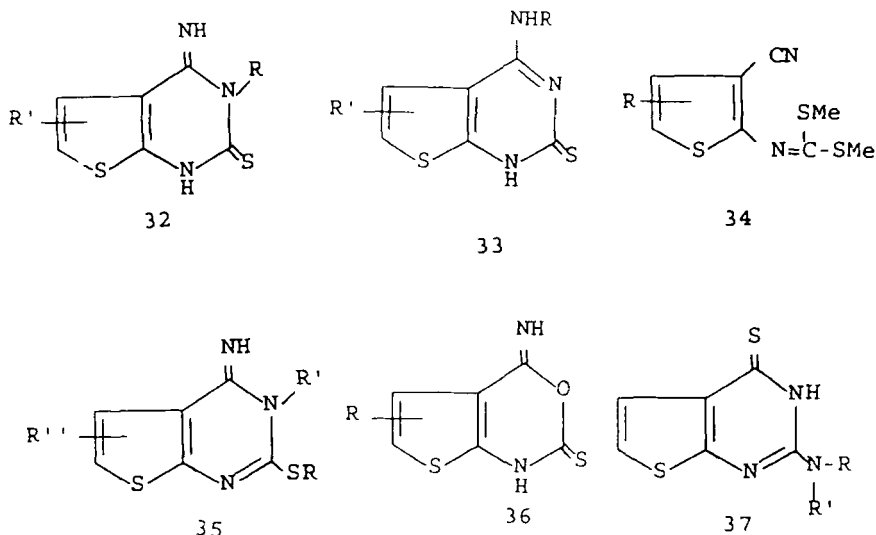
Cyclization of **24** with *N*-cyano-bis(methylthio)methyleneamine **29** and primary amines gave the corresponding 2-cyanoamino-4-oxo derivatives **30** (*R* = CN) [87EGP(D)249023; 93PHA347].

Treating 2-aminothiophene-3-carboxamides **31** with trichloroacetonitrile in basic media gave the corresponding **28** [89ZN(B)488].

5. Condensation with Amino-Thioxopyrimidines

Condensation of **17** with thiourea gave the corresponding 4-imino-thieno[2,3-*d*]pyrimidine-2(1*H*)-thiones **32** (92PS93; 93PHA347). With PhCONCS, however, the 3-benzoyl-4-imino derivative **32** (*R* = C(=O)Ph) (92PS93) or the 4-amino derivatives **33** (*R* = H) [89AP227; 91EGP(D)287503] were obtained.





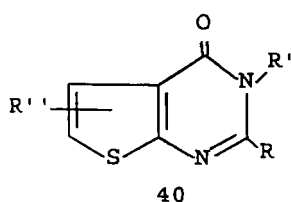
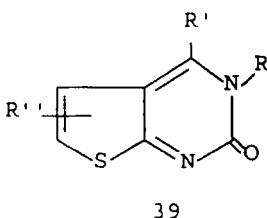
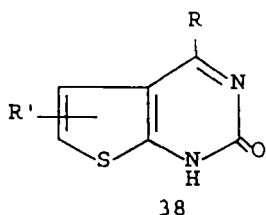
3-Cyano-2-bis(methylthio)methyleneaminothiophenes **34** and arylamines gave the corresponding 2-methylthio-3-aryl derivatives **35** ($R = \text{Me}$, $R' = \text{Ar}$) [89IJC(B)642], while 4-iminothieno[2,3-*d*]thiazine-2(1*H*)-thiones **36** with ammonia gave the corresponding 4-imino derivatives **32** [89-IJC(B)642] or the 4-amino derivatives **33** [90IJC(B)1070].

The action of thiocyanates of **25** gave the 2-substituted amino-4-thioxo-thienopyrimidines **37** (80LA699).

6. Condensation with Oxopyrimidines

With urethane [73GEP(O)2323149; 75BCJ147] or urea [68CR(C)697; 75JAP75/11398], 2-amino-3-acylthiophenes **13** ($R' = \text{H}$) gave the corresponding thieno[2,3-*d*]pyrimidin-2(1*H*)-ones **38**. Compounds **13** ($R' = \text{COCCl}_3$) and ammonium acetate also formed **38** [73GEP(O)2310016]. Condensation of **13** ($R = \text{H}$) with methylisocyanate gave the 3-methylthieno[2,3-*d*]pyrimidin-2(3*H*)-ones **39** (76BCJ1395).

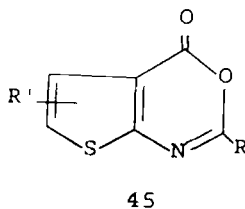
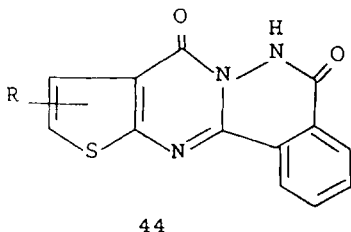
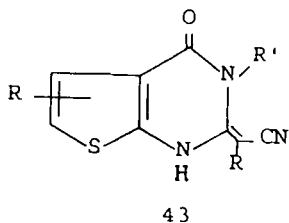
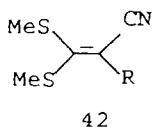
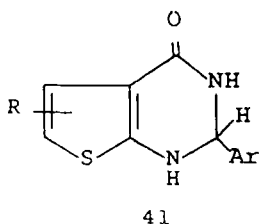
Cyclization of 2-formamidothiophene-3-carboxamide **31** ($R = \text{CHO}$) with NaOMe produced thieno[2,3-*d*]pyrimidin-4(3*H*)-one **40** ($R = R' = \text{H}$) [53JOC138; 67CR(C)207]. Other 2-acylaminothiophene-3-carboxamides **31** were cyclized to give the corresponding **40** ($R' = \text{H}$ or aryl) [75BSF587, 75BSF2483; 76AP908; 76M669; 77USP4054656; 78BEP859818; 79GEP(O)2746750, 79JMC505; 83PHA136; 89YZ464]. Also, 2-amino-3-cyanothiophenes **17** with formic acid and NaOAc or polyphosphoric acid (92MI2) gave **40** ($R' = \text{H}$), as did cyclization of 2-acylamino-3-cyanothio-



phenes **23** with EtOH/HBr [69JCS(C)1937; 75BSF587; 83MI1]. Condensation of 2-aminothiophene-3-carboxylates **24** with formamide yielded **40** ($R = R' = H$) [66URP179323; 67CR(C)207; 67KGS459; 68AG(E)136; 68LA143; 71IJC1209; 75BSF587; 76IJC(B)537; 81JHC1277; 83ZC179; 84MI2; 86KFZ39, 86MI1; 93PHA192]. The reaction of compounds **24** with nitriles and dry HCl afforded the corresponding **40** ($R' = H$) [68AG(E)136; 80JHC1497; 83MIP1; 84JHC375, 84MI2; 85IJC(B)432, 85JHC825; 86EGP(D)234268, 86EGP(D)234269; 87JHC581; 87USP4701528; 88MI2; 89IJC(B)1039, 89PHA790, 89ZN(B)488]. Also, the reaction of **24** with iminoesters [$RC(OR=NH)$] gave derivatives of **40** ($R' = H$) [68AG(E)136, 68LA143; 72GEP(O)2117658; 83PHA269].

Amino amide **31** ($R = H$) with nitriles (RCN) in dioxane and dry HCl gave **40** ($R' = H$) (80JHC1497), and treatment of **31** ($R = H$) with triethylorthoformate [71JHC1209; 76IJC(B)537; 84PHA19] or with acetyl chloride [68CR(C)697] gave the corresponding **40**.

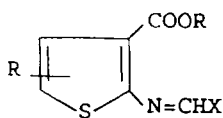
Condensation of **31** ($R = H$) with cinnamaldehyde gave the 2-styryl derivative **40** ($R = CH=CHPh$, $R' = H$) (85JHC825). With other aromatic aldehydes, however, the tetrahydro derivatives **41** were obtained (71MIP1). Condensation of **31** ($R = H$) with acetylacetone gave the 2-methyl derivatives **40** ($R = Me$, $R' = H$) (84MI1), and **31** ($R = R' = H$) with 3,3-bis(methylthio)acrylonitriles **42** in DMF/ Na_2CO_3 gave the 2-methylene derivatives **43** [87EGP(D)249021, 87EGP(D)249022; 93PHA347]. Cyclocondensation of **31** ($R = H$, $R' = NH_2$) with phthalic anhydride gave the corresponding condensed thienopyrimidinone **44** (91JHC545, 91JHC891). Heating 2-acylamino-3-cyanothiophenes **23** with P_2O_5 , N,N -dicyclohexylamine hydrochloride, and aromatic amines formed the corresponding 3-aryl derivatives **40** ($R = H$; $R' = Ar$) (89CS261). Other syntheses of 3-aryl derivatives **40** involved heating 2-acylaminothiophene-3-carboxylates **24** ($R = acyl$) with aromatic amines and $POCl_3$ in toluene (68MI1). Also, condensation of **24** with RNH_2 in the presence of P_2O_5 and N,N -dicyclohexylamine at $180^\circ C$ yielded **40** (81CS135). Condensation of 2-acylaminothiophene-3-carboxylates **24** with N,N' -dimethylphosphoramidate gave the 3-methyl derivatives **40** ($R' = Me$) [78ACS(B)303]. Condensation of amines ($R'NH_2$) with the thieno[2,3-*d*]oxazinones **45** gave also the correspond-



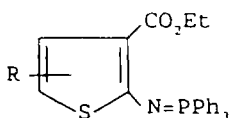
ing **40** (68LA219; 74MI2; 76MI1; 76MIP1; 81JIC982; 87JAP62/132884). Condensation of 2-aminothiophene-3-carboxylates **29** with cyclic lactams gave the condensed systems **40** [$R, R' = (CH_2)_n$, $n = 3-5$] (88DOK35). Heating **23** with H_2O_2 in basic medium gave **40** ($R = CH=CHPh$, $R' = H$) (90JMC1721).

Condensation of hydrazine with ethyl 2-ethoxymethyleneamino-3-thiophenecarboxylates **46** ($X = OEt$) or with 2-acylaminothiophenecarboxylates **24** gave the corresponding 3-amino derivatives **40** ($R' = NH_2$) [72MIP1; 76AP914; 81KFZ40; 85IJC(B)432; 88MI2]. Compounds **40** ($R' = NH_2$) were deaminated with nitrous acid to give the corresponding **40** ($R' = H$) [85IJC(B)432]. Condensation of 2-aminothiophene-3-carboxyhydrazides **31** ($R = H$, $R' = NH_2$) with formic acid gave the 3-formamido derivatives **40** ($R = H$, $R' = NHCHO$) (88CB573). The hydroxy derivatives **40** ($R' = OH$) were obtained by the condensation of **46** ($X = NMe_2$) with hydroxylamine [81JAP(K)81/08389, 81JAP(K)81/34683, 81JAP(K)81/53681]. Condensation of the formamidine **46** ($X = NMe_2$) with ammonia or amines gave **40** (71MI1). Condensation of 2-ethoxymethylenethiophene-3-carboxylates **46** ($X = OEt$) with arylamines gave the corresponding 3-aryl derivatives **40** ($R = H$, $R' = Ar$) [85IJC(B)432].

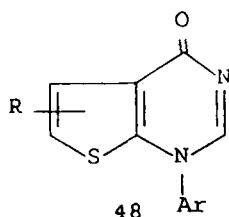
Treatment of the iminophosphoranes **47** first with $PhNCO$ and then with methanol gave compounds **40** ($R = OMe$, $R' = Ph$), while treatment with diphenylketene and then butylamine gave compounds **40** ($R = NHBu$, $R' = CHPh_2$) (93T581). Cyclization of 2-arylaminothiophene-3-carboxamides **31** ($R = Ar$) with triethylorthoformate in acetic anhydride gave the corresponding thieno[2,3-*d*]pyrimidin-4(1*H*)-ones (84JPR917).



46



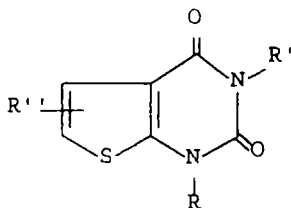
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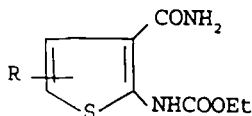
48

7. Condensation with Dioxypyrimidines

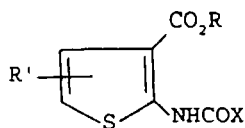
Thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **49** ($R = R' = H$) were prepared by the condensation of 2-aminothiophene-3-carboxylates **24** with potassium cyanate [73GEP(O)2200764; 81JMC376], urea [68CR(C)128; 81JMC376], or isocyanates (69CB3698; 71IJC1209; 77MI1). Cyclization of the 2-ethoxycarbamoylthiophene-3-carboxamides **50** (83AKZ108) or the urea derivatives **51** ($X = NHR$) (88JMC1786; 89USP4835157) in basic medium also gave **49**. Condensation of **24** arylureas gave either **49** ($R = R' = H$) or the 3-aryl derivatives **49** ($R = H, R' = Ar$) (91MI1). Heating the 2-ethoxycarbamoylthiophene-3-carboxylates **51** ($X = OEt$) with primary amines ($R'NH_2$) gave the 3-substituted derivatives **49** ($R = H$) (89MIP2). Cyclization of **51** ($X = NHR$) with arylureas in basic media afforded the 3-aryl derivatives **49** ($R = H, R' = Ar$) (83AKZ108). The reaction of 2-anilinothiophene-3-carboxylates **24** ($R = Ph$) with methylisocyanate and NaH in toluene gave the 3-methyl-1-phenyl derivative **49** ($R = Ph, R' = Me$) (74IJC1). The 3-hydroxy derivative **49** ($R = R'' = H, R' = OH$) was prepared together with its isomeric thieno[3,2-*d*]pyrimidine derivative by



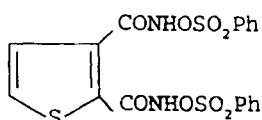
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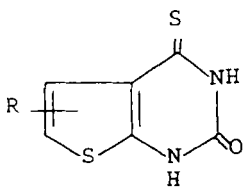


52

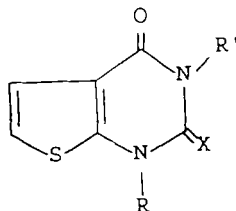
a modified Lossen rearrangement of thiophene-2,3-dicarbohydroxamate **52** (75JOC172).

8. Condensation with Oxo-Thioxopyrimidines or Oxo-Selenoxopyrimidines

Thieno[2,3-*d*]pyrimidin-2(1*H*)-one-4(3*H*)-thiones **53** were obtained by condensation of 2-amino-3-cyanothiophenes **17** with carbonyl sulfide (COS) in a basic medium (81JOC3941). Thieno[2,3-*d*]pyrimidin-4(3*H*)-one-2(1*H*)-thiones **54a** ($R = R' = H$) were obtained by condensation of 2-aminothiophene-3-carboxylates **24** with ammonium or potassium thiocyanates or with thiourea [72GEP(O)2210503; 73MI593; 84JHC375; 90DOK32] or arylthioureas (91MI1), as well as by the action of PhCONCS on **24** (74KGS486, 74URP455105) and by condensation with formamide and sulfur (90DOK32). Also, heating 2-aminothiophene-3-carboxamides **31** ($R = H$) with thiourea gave **54a** ($R = R' = H$) (73MI1593). The 3-substituted derivatives **54a** ($R = H$) were obtained by cyclization of the thiourea derivatives **55a** [71JHC1051; 73KGS1289, 73M1593; 74M558; 76JPS660; 71IJC(B)575; 81JHC1277; 82EUP43054; 86EGP(D)240892; 87PHA160; 88DOK35; 89PHA153; 90PHA827; 91EGP(D)287503]. Compounds **55a** were obtained either by the action of RNCS on **24** ($R = H$) or by reacting **24** with thiophosgene to give isothiocyanates **56**, which then afforded **55a** by the action of amines ($R'NH_2$). Similarly, cyclization of the seleno derivatives **55b** gave the corresponding 2-seleno derivatives **54b** (77KGS753).

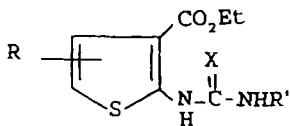


53



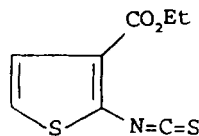
54a (X=S)

54b (X=Se)

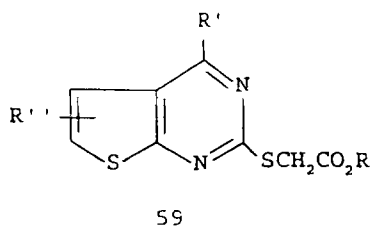
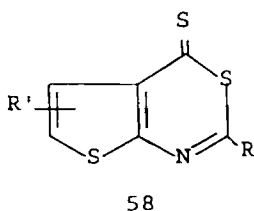
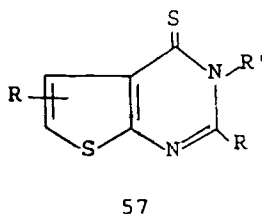


55a (X=S)

55b (X=Se)



56



9. Condensation with Thioxopyrimidines

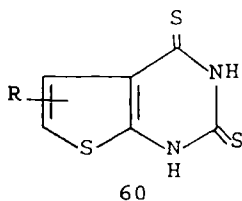
Thieno[2,3-*d*]pyrimidine-4(3*H*)-thiones **57** ($R = R' = H$) were obtained by condensation of 2-amino-3-cyanothiophenes **17** with formamide and NaSH (88JPR585). The 2-substituted derivatives **57** ($R' = H$) were prepared by the condensation of **17** with thioamides ($RCSNH_2$) [69JCS(C)1937]. Condensation of $R'NH_2$ with thieno[2,3-*d*]thiazinethiones **58** gave the corresponding thienopyrimidinethiones **57** ($R' = H$, alkyl, NH_2 , OH) with the same R' [86EGP(D)234677; 86PHA96]. The 2-mercapto derivatives **59** were obtained by condensing 2-acylamino-3-benzoylthiophenes **13** ($R = COCH_2Br$) with KSCN in alcohols [77JAP(K)77/46095].

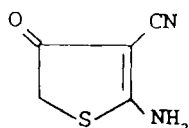
10. Condensation with Dithioxopyrimidines

Thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dithiones **60** were obtained by reacting 2-amino-3-cyanothiophene **17** with CS_2 in pyridine (88JPR585) or with EtOCSSK (72S268).

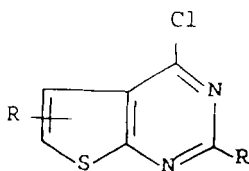
11. Condensation with Chloropyrimidines

Heating 2-amino-3-cyanothiophen-4(5*H*)-one **61** with $POCl_3$ gave 4,5-dichlorothieno[2,3-*d*]pyrimidine **62** (91EUP447891). Condensation of derivatives of **17** with haloacetonitriles and dry HCl gave the corresponding 4-chloro derivatives **62** ($R = CHClR$) (83TL4611).





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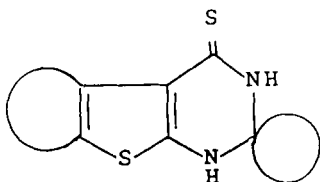
62

C. FROM OTHER STARTING MATERIALS

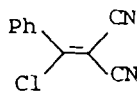
The base-catalyzed reaction of cycloalkanones with sulfur and cyanoacetamide gave 1,2-dihydro-2-spirothieno[2,3-*d*]pyrimidine-4(3*H*)-thiones **63** (90JPR223).

The reaction of α -cyano- β -chlorocinnamionitrile **64** with KSCN, ROH, and active bromomethylene compounds (BrCH_2X) gave the thieno[2,3-*d*]pyrimidine derivatives **65** [89EGP(D)273441]. Condensation of tetracyano-1,4-dithiin **66** with NaCN in THF produced 4,5,6-tricyanothieno[2,3-*d*]pyrimidine-2-thiolate **67** (80JOC5113).

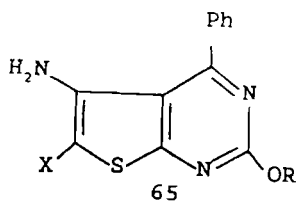
3-Amino-4-methyl-6-phenylthiazolo[5,4-*d*]pyrimidine **68** with chloroacetone gave the 5-amino-6-acetylthieno[2,3-*d*]pyrimidine **69** [88JCR(M)326, 88JCR(S)46].



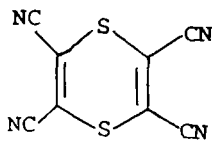
63



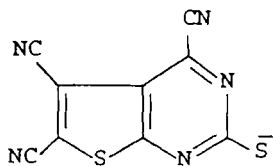
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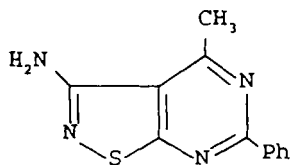
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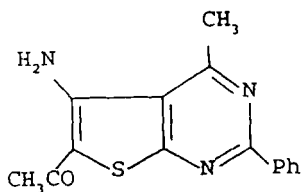
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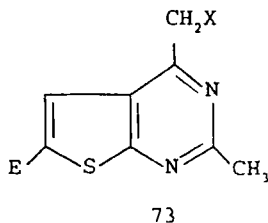
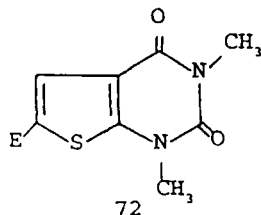
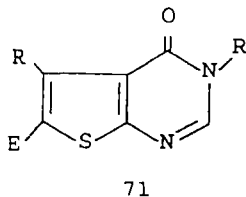
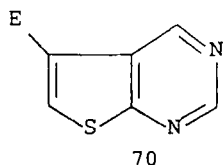
IV. Reactions of Thieno[2,3-*d*]pyrimidines

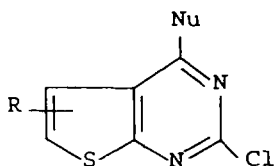
A. REACTIONS WITH ELECTROPHILIC REAGENTS

Nitration of thieno[2,3-*d*]pyrimidine **1** gave the 5-nitro derivative **70** ($E = \text{NO}_2$) (80JHC1019). Other studies of electrophilic reactions of substituted **1** have been reported [68CR(C)697; 76BSF761; 77BSF676]. However, bromination and nitration of thieno[2,3-*d*]pyrimidin-4(3*H*)-one was reported to give the corresponding 5(or 6)-bromo **71** (R or $E = \text{Br}$) and 5(or 6)-nitro **71** (R or $E = \text{NO}_2$) derivatives, respectively [68CR(C)1706]. Bromination, nitration, and Vilsmeier-Haack reactions of 1,3-dimethylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione gave the corresponding 6-bromo **72** ($E = \text{Br}$), 6-nitro **72** ($E = \text{NO}_2$), and 6-formyl **72** ($E = \text{CHO}$) derivatives, respectively (90JHC717). The action of *sec*-butyllithium on thieno[2,3-*d*]pyrimidine **73** ($E = X = \text{H}$) followed by ArSCl or Ar_2S yields the 6-arylsulfenyl derivatives **73** ($E = \text{ArS}$, $X = \text{H}$) (90HCA797).

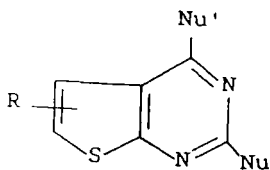
B. REACTIONS WITH NUCLEOPHILIC REAGENTS

The action of organolithium compounds on 2-(2-thienyl)thieno[2,3-*d*]pyrimidine was reported (77BSF676). Studies of other nucleophilic reagents (including amines, alcoholates, thiolates, and carbanions) have been carried out, particularly on the derivatives having halogen atoms at the 2- and/or 4-positions or other leaving groups such as SR or $\text{S(O)}_n\text{R}$. The nucleophile displaces these groups to give the corresponding functionalized thieno[2,3-*d*]pyrimidines. In case of the 2,4-dichlorothieno[2,3-*d*]pyrimidines, the nu-





74

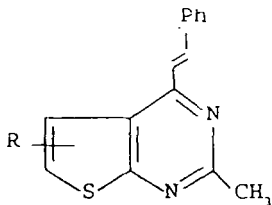


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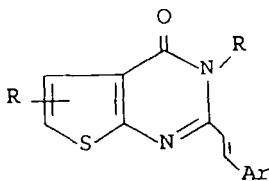
cleophiles first attack the 4-position to give the 2-chloro derivatives **74**, which then react further with the same or other nucleophiles to afford the disubstituted derivatives **75** [67CR(C)207; 68CR(C)128; 71IJC1209, 71JHC1051; 72GEP(O)2117658, 72GEP(O)2121950, 72MI1; 72MI2, 72MIP2; 73GEP(O)2200764; 75BSF592, 75BSF815, 75BSF2483; 77BEP859818; 78ACS(B)303; 81JHC1277; 83EUP82023, 83PHA269; 84JHC375; 85EGP(D)226893, 85EUP150469; 86EGP(D)237663, 86KFZ39, 86MI1, 86MI4, 86PHA23; 87EGP(D)245666, 87EGP(D)245667, 87EGP(D)248593, 87JAP(K)6200427, 87KFZ197; 89YZ464; 91IJC(B)618, 91PHA422; 92PHA20].

C. REACTIVITY OF THE 2- AND 4-METHYL GROUPS

Condensation of **73** ($X = H$) with benzaldehyde in acetic anhydride gave the 4-styryl derivative **76**, while **73** ($X = H$) was preferentially converted to the corresponding 4-substituted methyl derivatives **73** ($X = Br, NO, OH$) upon treatment with $Br_2/CHCl_3$, $PrONO$ or SeO_2 , respectively (89YZ642). Condensation of the 2-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones with aromatic aldehydes and $ZnCl_2$ or under acidic or basic conditions yielded the corresponding 2-styryl derivatives **77** [85EGP(D)225993, 85JHC825; 87PHA131]. Compounds **77** were also obtained via Wittig reactions of the aromatic aldehydes with the appropriate ylides (85JHC825).



76



77

D. ACTION OF REDUCING AGENTS

Catalytic reduction converts the 4-chloro derivative **62** ($R = H$) to the parent compound **1** (76BSF761).

Sodium borohydride reduction of the pyrimidine ring was effected using $NaBH_4$. Thus, thieno[2,3-*d*]pyrimidin-4(3*H*)-one and its isomeric 2(3*H*)-ones were reduced to the corresponding tetrahydro derivative **78** and **79** (73MI1; 80CPB3172). Other substituted thieno[2,3-*d*]pyrimidines were reduced to the corresponding 3,4-dihydro derivatives **80** [81JHC67, 81JMC376; 82JAP(K)82/77687].

Raney Nickel was used for the desulfurization of the thiophene ring, thereby converting derivatives in this class of compounds into substituted pyrimidines [66AG(E)131; 67JOC2376; 76M1193].

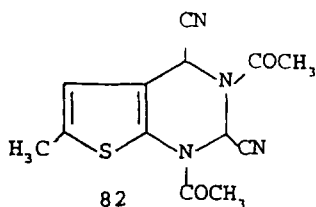
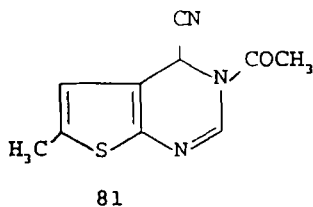
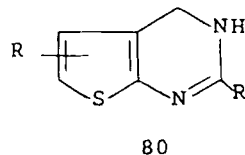
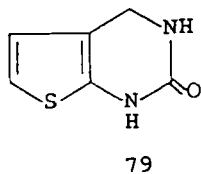
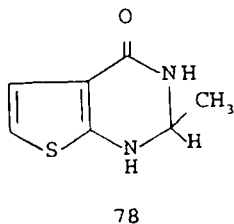
Zinc in ethanol and acetic acid replaces the 4-chloro substituent by hydrogen (86JHC545).

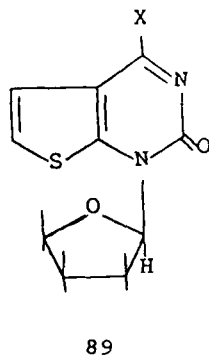
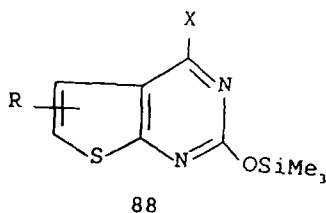
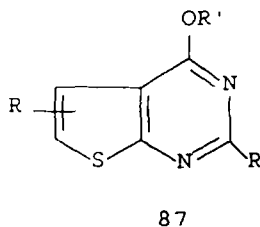
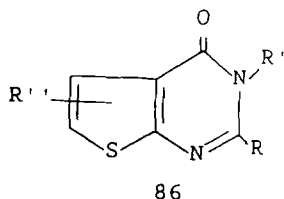
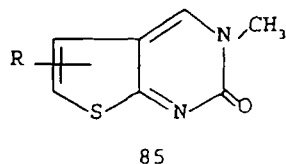
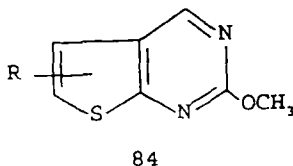
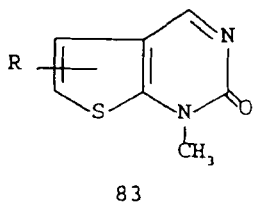
With tributyltin cyanide in the presence of benzoyl chloride or acetyl chloride, 6-methylthieno[2,3-*d*]pyrimidine gave the mono- or di-Reissert adducts **81** and **82**, respectively (86JHC545).

E. REACTIONS OF THE OXO DERIVATIVES

1. Alkylation

Methylation of 2-oxo derivatives with methyl iodide and NaH produced the corresponding 1-methyl **83**, 2-methoxy **84**, and 3-methyl **85** derivatives

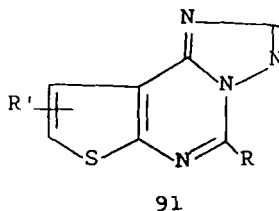
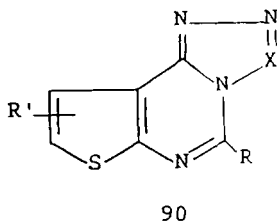




[73GEP(O)2323149; 75BCJ147]. The 1-methyl derivatives **83** were isolated only when the reaction was carried out in NaOMe (75JAP75/11398). Alkylation of the 4-oxo analogs gave the corresponding 3-alkyl derivatives **86** [68CR(C)128; 75BSF587; 86PHA661; 89JOC990], the 4-alkoxy derivative **87**, or a mixture of both (71JHC1051). Alkylation of the 4-oxo and 2,4-dioxo derivatives using phase-transfer catalysts afforded the corresponding 3-alkyl and 1,3-dialkyl derivatives, respectively (77MI1; 83PHA135; 86PHA661). Treatment of derivatives of thieno[2,3-*d*]pyrimidin-2(1*H*)-ones with hexamethyldisilazane catalyzed with ammonium sulfate gave the silyloxy derivatives **88**, which were ribosylated to the 1- β -ribosyl derivatives **89** [80JCS(P1)1853; 85JMC423].

2. Reaction with Phosphorus Halides or Thionyl Chloride

The 2- and/or 4-chloro and 2,4-dichloro derivatives were obtained by the action of POCl₃ on the corresponding oxo derivatives [67CR(C)207;



72GEP(O)2050815; 72MI1; 75BSF2483; 86EGP(D)237663]. Thionyl chloride and DMF were used to prepare the 4-chloro derivatives from the corresponding 3-unsubstituted 4-oxo derivatives (87KFZ197).

F. REACTIONS OF THE THIOXO DERIVATIVES

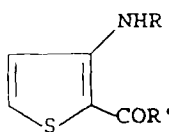
Alkylation of the 2-thioxo derivatives with alkyl halides in basic medium gave the corresponding *S*-alkyl derivatives [74KGS486, 74M452, 74M863, 74M1258; 81JHC1277; 86EGP(D)240892; 87PHA160; 89KGS413; 90DOK32, 90PHA493; 91EGP(D)287503], and alkylation of the 4-thioxo derivatives gave the *S*-alkyl derivatives [68CR(C)128; 75JHC921]. With acrylonitrile, the *S*-cyanoethyl and 3-*N*-cyanoethyl derivatives were generated (75JHC921).

G. REACTIONS OF THE HYDRAZINO DERIVATIVES

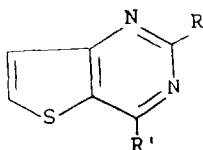
The 4-hydrazino derivatives undergo cyclocondensation reactions to tricyclic systems **90** ($X = N$) with nitrous acid [68CR(C)128, 68CR(C)697, 68C(C)1706; 75BSF2483; 82IJC(B)666]. With formic acid or ethyl orthoformate they gave **90** ($X = CH$) or the rearrangement products **91** [68CR(C)128, 68CR(C)697, 68CR(C)1706; 71IJC1209; 75BSF815, 75BSF2483, 75JHC525; 81JHC43; 87JHC1125]. Oxidation of the 4-hydrazino group with HgO or oxygen in NaOEt generated 4-unsubstituted derivatives ($NHNH_2$ is replaced by H) [68CR(C)128; 75BSF2483; 76BSF761].

V. Synthetic Approaches to Thieno[3,2-*d*]pyrimidines

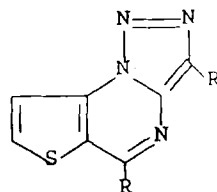
Most of the reported syntheses of this class of compounds start with thiophene derivatives.



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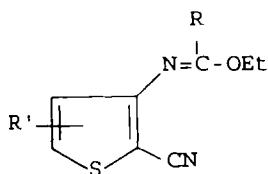
94

A. THIENO[3,2-*d*]PYRIMIDINES AND THEIR 2- AND 4-ALKYL DERIVATIVES

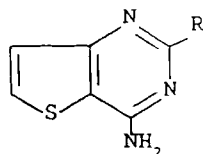
Condensation of 3-acylamino-2-acylthiophenes **92** ($R = \text{COR}$) with ammonium formate gave the corresponding thienopyrimidines **93** ($R, R' = \text{H}$ or Me) [74CR(C)1513; 76BSF151]. The substituted methyl derivatives of **93** ($R = \text{XCH}_2$) were prepared by the action of nucleophilic reagents on 1,2,3-triazolo[3,4-*a*]thieno[3,2-*d*]pyrimidines **94** (80JHC1771).

B. 4-AMINO- AND 2,4-DIAMINOTHIENO[3,2-*d*]PYRIMIDINES

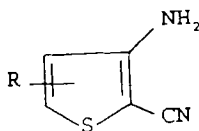
3-Ethoxymethylene-2-cyanothiophenes **95** with ammonia (62LA90) or sodamide (86JHC1757) gave the corresponding 4-aminothieno[3,2-*d*]pyrimidines **96**. The 2-substituted derivatives of **96** were prepared from **94** ($R = \text{NH}_2$) with nucleophilic reagents (80JHC1771). 3-Amino-2-cyanothiophenes **97** on cyclization with guanidine gave the 2,4-diaminothieno[3,2-*d*]pyrimidines **98** (86JHC1757).



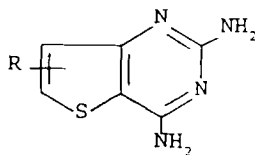
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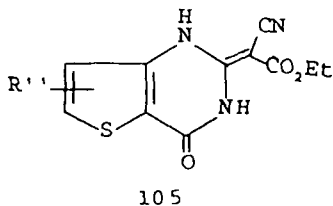
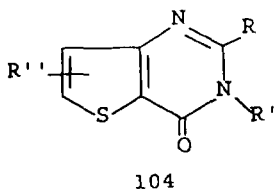
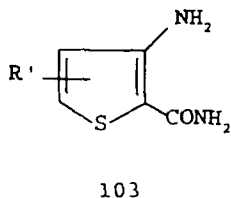
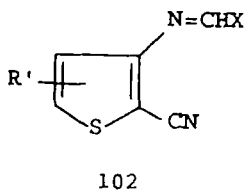
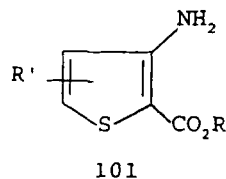
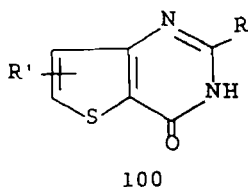
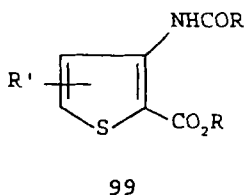
97



98

C. 4-Oxothieno[3,2-*d*]pyrimidines

Cyclization of 3-formylaminothiophene-2-carboxylate **99** with methanolic ammonia gave thieno[3,2-*d*]pyrimidin-4(3*H*)-one **100** ($R = H$) (53JOC138), which represents the first reported example of this class of compounds. Improved yields of **100** were achieved by heating **99** with ammonia in methanol at 120°C or with ammonium formate and formamide at 140°C [67CR(C)100; 70BSF3630]. Compounds **100** were also obtained by heating 3-aminothiophene-2-carboxylate **101** with formamide (67BRP1057612; 68LA143; 79YZ1081; 85IZV1858; 86MI1) or with nitriles (RCN) and HCl (92EUP502725). Condensation of 3-methyleneiminothiophene-2-carboxylates **102** ($X = OEt$ or NMe_2) with ammonia (82JOC4633; 85IZV1858) or primary amines (92BSB445) or condensation of 3-aminothiophene-2-carboxamide **103** with triethyl orthoformate (62LA90; 82JOC4633) also gave **100**. Heating **101** with iminoesters afforded the corresponding 2-substituted derivatives **100** [68AG(E)136, 68LA143; 71GEP(O)1959402, 71GEP(O)1959403]. Condensation of **99**



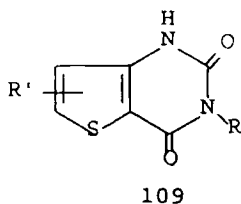
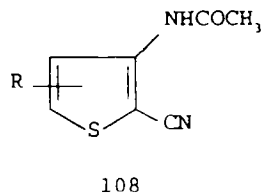
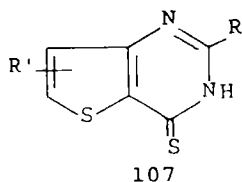
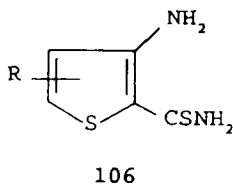
($R = R' = \text{Me}$) with arylamines in the presence of POCl_3 gave the corresponding 3-aryl derivatives **104** ($R' = \text{Ar}$) (68LA219, 68MI1), and with methylamine they gave the 3-methyl derivatives **104** [91EGP(D)295381]. Condensation of **101** and phenylacetonitrile with sodium in toluene (67BRP1057612) or with AlCl_3 [68AG(E)136] gave **100** ($R = \text{CH}_2\text{Ph}$, $R' = \text{H}$), and **101** with the sodium salt of ethyl dicyanoacetate gave the 2-alkylidene derivative **105** (91HCA579). Also, some 2-substituted methyl derivative of **100** ($R = \text{CH}_2\text{Nu}$) were obtained by the action of nucleophilic reagents on the triazolothienopyrimidine **94** (80JHC1771).

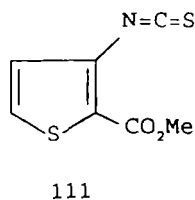
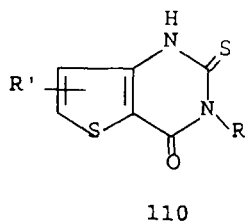
D. 4-THIOXOTHIENO[3,2-*d*]PYRIMIDINES

3-Aminothiophene-2-thiocarboxamide **106** and orthoesters gave the 4-thione **107** ($R = \text{H}$) (86JHC1757). The 2-methyl derivative **107** ($R = \text{Me}$) was obtained by reacting 3-acetamido-2-cyanothiophene **108** with sodium hydrogen sulfide (86JHC1757).

E. 2,4-DIOXOTHIENO[3,2-*d*]PYRIMIDINES

Heating esters **101** with urea at 200°C generated the corresponding diones **109** ($R = \text{H}$) and with phenylisocyanate gave the 3-phenyl derivative **109** ($R = \text{Ph}$) (67BRP1057612). Cyclization of urea derivatives **99** ($R = \text{NHR}$) gave the diones **109** (88JMC1786; 89USP4835157). Rearrangement of 2,3-thiophenedicarbohydroxamate **52** produced a mixture of **109** ($R = \text{PhSO}_3$) and the isomeric derivative **49** (75JOC172).





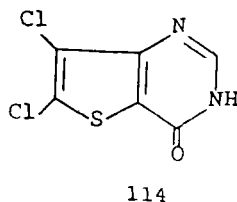
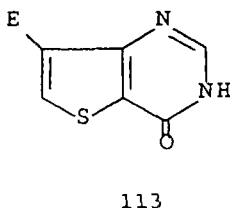
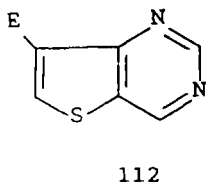
F. 4-Oxo-2-thioxothieno[3,2-*d*]pyrimidines

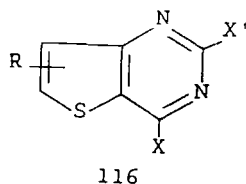
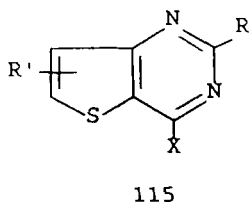
The action of potassium thiocyanate on **101** gave the corresponding derivative **110** (67BRP1057612). The 3-ethoxycarbonylmethyl derivative **110** ($R = CH_2COOC_2H_5$) was obtained by the action of ethyl glycinate on methyl 3-isothiocyanato-2-phenylthiocarboxylate **111** (80EUP43054).

VI. Reactions of Thieno[3,2-*d*]pyrimidines

A. REACTIONS WITH ELECTROPHILIC REAGENTS

Electrophilic reagents attack the thiophene ring mainly at position 7. Thus, bromination, chlorination, and nitration of the parent compound **2** yielded the corresponding 7-substituted derivatives **112** ($E = Br, Cl, NO_2$) [CR(C)697; 71T487]. The action of these electrophilic reagents on 2-(2-thienyl)thieno[3,2-*d*]pyrimidine has also been reported (77BSF676). However, other electrophilic substitution reactions of **2**, such as sulfonation, iodination and Friedel-Crafts acylation, have been unsuccessful (71T487). The 7-substituted derivatives **113** ($E = Br, NO_2$) were obtained by electrophilic bromination and nitration of **100** ($R = R' = H$). However, chlorination of the latter gave the corresponding 6,7-dichloro derivative **114** (70BSF3630).



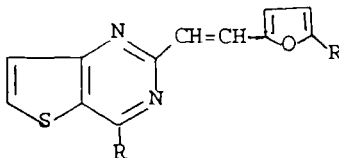


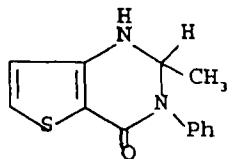
B. REACTIONS WITH NUCLEOPHILIC REAGENTS

Nucleophilic reagents attack the pyrimidine ring containing a suitable leaving group to give the corresponding substituted derivatives. Thus, amines, alkoxides, phenoxides, and NaSH react with the 4-chloro derivatives **115** ($X = \text{Cl}$) to give the corresponding 4-substituted derivatives **115** ($X = \text{Nu}$) [67BRP1057612, 67CR(C)100; 68CR(C)1706; 70BSF360; 71GEP(O)1959403, 71T487; 72GEP(O)2050814, 72GEP(O)2050815, 72GEP(O)2050816; 86MI1]. Nucleophilic reagents first attack the dichloro derivatives **116** ($X = X' = \text{Cl}$) at the 4-position to give the corresponding 2-chloro derivatives **116** ($X' = \text{Cl}$, $X = \text{Nu}$), which then react further with the same or a different nucleophile to give the corresponding 2,4-disubstituted **116** ($X = \text{Nu}$, $X' = \text{Nu}'$, where Nu , $\text{Nu}' = \text{OR}$, NHR , NRR' , SH) [67BRP1057612; 71GEP(O)1940572, 71GEP(O)2003714; 72GEP(O)2032686, 72GEP(O)2032687, 72GEP(O)2039662, 72GEP(O)2058085, 72GEP(O)2058086; 73GEP(O)2137341, 73GEP(O)2215299]. The action of organolithium compounds on 2-(2-thienyl)thieno[3,2-*d*]pyrimidine has also been studied (77BSF676).

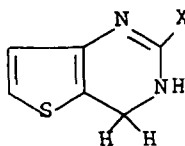
C. REACTIVITY OF THE 2-METHYL GROUP

Condensation of 2-methylthieno [3,2-*d*]pyrimidines with furfural in acetic anhydride gave the 2-furylvinyl derivatives **117** [72GEP(O)2039662, 72GEP(O)2039663].

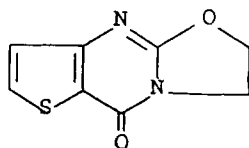




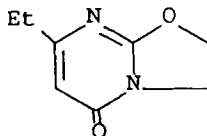
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D. ACTION OF REDUCING AGENTS

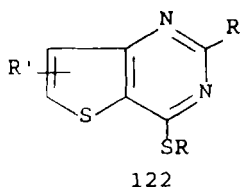
Reduction of **104** with NaBH_4 gave the corresponding 1,2-dihydro derivative **118** (73MI1). Reduction of **116** ($\text{X} = \text{X}' = \text{Cl}$) with NaBH_4 gave the corresponding 2-chloro-3,4-dihydro derivatives **119**, which were used to prepare other 2-substituted 3,4-dihydrothieno[3,2-*d*]pyrimidines through nucleophilic displacement (81JHC67, 81JMC376).

The thienopyrimidine derivative **120** undergoes desulfurization to the corresponding pyrimidine derivative **121** by the action of Raney Ni (89CPB1197).

E. REACTIONS OF THE OXO DERIVATIVES

Alkylation of thieno[3,2-*d*]pyrimidin-4(3*H*)-one **100** ($\text{R} = \text{R}' = \text{H}$) gave the corresponding 3-alkyl derivatives **104** [67CR(C)100; 70BSF3630].

The 4-chloro and 4-bromothieno[3,2-*d*]pyrimidines **115** ($\text{X} = \text{Cl}$ or Br) were readily obtained by the action of POCl_3 or POBr_3 on **100** [67BRP1057612, 67CR(C)100; 70BSF3630; 71GEP(O)1940572, 71T487]. Similarly, the 2,4-dichlorothieno[3,2-*d*]pyrimidines **116** ($\text{X} = \text{X}' = \text{Cl}$) were obtained by the action of POCl_3 on the diones **109** ($\text{R} = \text{H}$) (67BRP1057612). Thionyl chloride in DMF was also used to convert **100** to **115** ($\text{X} = \text{Cl}$) (86MI1).



F. REACTIONS OF THE THIOXO DERIVATIVES

Alkylation of the 4-thioxo derivatives **107** ($R = R' = H$) gave the 4-alkylthio derivative **122** (86JHC1757). The action of $POCl_3$ in *N,N*-dimethylaniline on **107** gave the 4-chloro derivative **115** ($X = Cl$) (86JHC1757).

VII. Synthetic Approaches to Thieno[3,4-*d*]pyrimidines

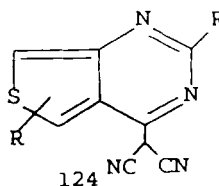
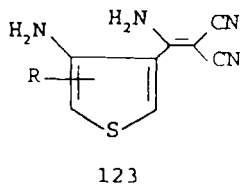
A. FROM THIOPHENE DERIVATIVES

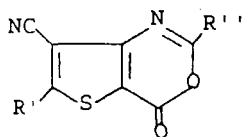
1. Condensation with Substituted Pyrimidines

Condensation of 3-amino-4-aminomethylenethiophene derivative **123** with aldehydes in DMF and piperidine gave the corresponding 2,4-disubstituted thieno[3,4-*d*]pyrimidines **124** [94JCR(S)484].

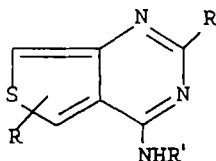
2. Condensation with Aminopyrimidines

Treatment of 7-cyanothieno[3,2-*d*]oxazin-4-ones **125** with primary amines yielded the corresponding 4-aminothieno[3,4-*d*]pyrimidines **126** [90EGP(D)282011]. Condensation of 4-cyano-3-ethoxymethylenethiophenes **127** with ammonium acetate also gave **126** ($R = R' = H$) (82S1056).

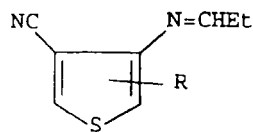




125



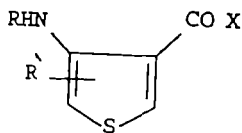
126



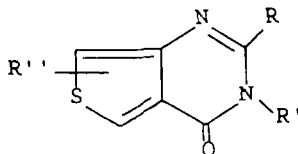
127

3. Condensation with Oxopyrimidines

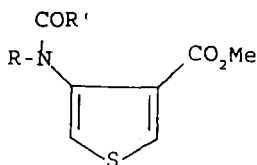
Cyclization of methyl 4-aminothiophene-3-carboxylate **128** ($X = \text{OMe}$, $R = R' = \text{H}$) with formamide at high temperature afforded thieno[3,4-*d*]pyrimidin-4(3*H*)-one **129** ($R = R' = \text{H}$) (75KGS914). The latter was also obtained by heating formyl derivative **128** ($R' = \text{CHO}$, $X = \text{OMe}$) with ammonium formate and formamide or by treating **128** ($R' = \text{CHO}$, $X = \text{NH}_2$) with NaOMe (53JOC138). The 3-substituted derivatives **129** were obtained by cyclocondensation of **128** ($R' = \text{H}$, $X = \text{NHR}$) with acetic anhydride (70CJC2709; 72USP3644357). Cyclization of **128** ($R' = \text{acyl}$, $X = \text{OH}$) with primary amines and POCl_3 also gave the derivatives **129** (72BEP769844). Heating **128** ($R = \text{H}$, $X = \text{NH}_2$) with triethyl orthoformate in acetic anhydride gave **129** ($R = R' = \text{H}$) (62LA90). The C7-ribosyl derivatives **129** ($R'' = 7\text{-ribosyl}$) (88TL3537) and the N1 ribosyl **131** ($R = \text{rigoxyl}$) (90MI4) were obtained by the action of ammonia on the appropriate ribosylated thiophene derivatives **128** ($X = \text{OMe}$, $R' = \text{acyl}$) and **130**, respectively.



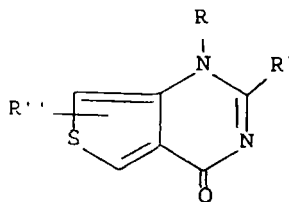
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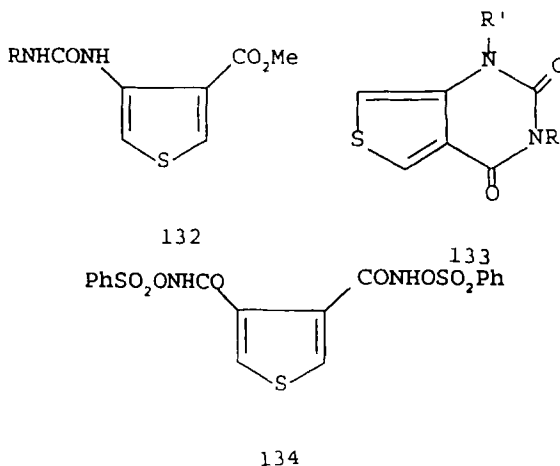
129



130



131



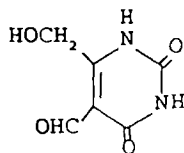
4. Condensation with 2,4-Dioxypyrimidines

Cyclization of 4-(methoxycarbonyl)thiophen-3-ylurea **132** ($R = H$) with ethanolic HCl gave the corresponding thieno[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **133** ($R = R' = H$) (72BEP769843; 88JMC1786). The 3-substituted derivatives of **133** were similarly prepared from the appropriate urea derivatives **128** ($R = CONHR$) (87USP4670560; 90JHC1761), as were the 1-aryl derivatives **133** ($R' = Ar$) [76JAP(K)76/88993]. Rearrangement of 3,4-thiophenedicarbohydroxamate **134** gave the corresponding 3-benzenesulfonyloxy derivative **133** ($R = OSO_2Ph$), which was hydrolyzed to the 3-hydroxy derivative **133** ($R = OH$) (75JOC172).

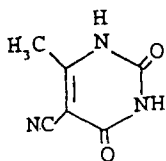
B. FROM PYRIMIDINE DERIVATIVES

1. Condensation with Thiophene

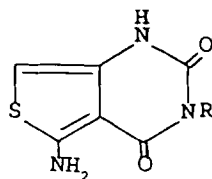
Cyclization of 6-(hydroxymethyl)pyrimidine-2,4(1*H*,3*H*)-dione-5-carboxaldehyde **135** with BF_3/Et_2O in thioacetic acid gave **133** ($R = R' = H$) (73TL2055).



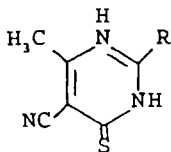
135



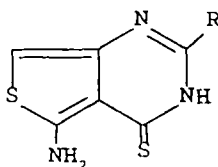
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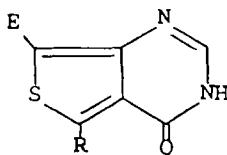
2. Condensation with Aminothiophenes

Cyclization of 5-cyano-6-methylpyrimidine-2,4(1*H*,3*H*)-diones **136** with elemental sulfur generated the corresponding 5-aminothieno[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **137** (90MI1; 91MI2). Similarly, cyclization of 5-cyanopyrimidine-4(3*H*)-thiones **138** with sulfur afforded the 5-amino-4-thioxo derivative **139** (90LA1215).

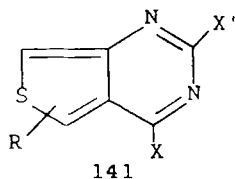
VIII. Reactions of Thieno[3,4-*d*]pyrimidines

A. REACTIONS WITH ELECTROPHILIC REAGENTS

Electrophilic chlorination, bromination, iodination, and nitration of **129** ($R = R' = R'' = H$) gave the corresponding 7-substituted **140** ($E = Cl, Br, I, NO_2$) and the 5,7-disubstituted derivatives **140** ($R = E = Br$) (74BSF1629).



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B. REACTIONS WITH NUCLEOPHILIC REAGENTS

The action of nucleophiles on the 2,4-dichlorothieno[3,4-*d*]pyrimidines **141** ($X = X' = \text{Cl}$) were shown to take place first at position 4 to give 2-chloro derivatives **141** ($X = \text{Nu}$, $X' = \text{Cl}$), which then react with the same or a different nucleophile to give disubstituted derivatives **141** ($X = \text{Nu}$, $X' = \text{Nu}'$, where Nu , $\text{Nu}' = \text{OR}$, NHR , NRR') (72BEP769843).

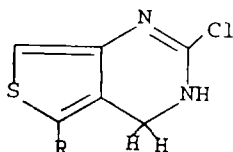
C. ACTION OF REDUCING AGENTS

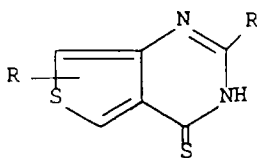
The action of NaBH_4 on **141** ($X = X' = \text{Cl}$) gave 2-chloro-3,4-dihydrothieno[3,4-*d*]pyrimidines **142**, which were used for the synthesis of 2-substituted dihydrothieno[3,4-*d*]pyrimidines via nucleophilic substitution reactions (81JMC376).

D. REACTIONS OF THE OXO DERIVATIVES

Alkylation of **129** ($R = \text{H}$) gave the corresponding 3-alkyl derivatives **129** [68CR(C)697; 74BSF1629]. Alkylation of **133** ($R = \text{H}$) with alkyl halides and NaH in DMF gave the 3-alkyl derivatives [76JAP(K)76/88993]. Similarly, 3-substituted **133** ($R' = \text{H}$) gave the corresponding 1-alkyl derivatives (90JHC1761). Selective alkylation at N1 was achieved using the 2,4-dimethoxybenzyl protecting group at N3, which then was readily removed in MeSO_3H (92SC3221).

Thiation of **129** ($R = \text{H}$) with P_2S_5 gave the 4-thioxo derivative **143** (74BSF1629).





143

The action of POCl_3 on the 2,4-diones **133** ($\text{R} = \text{R}' = \text{H}$) gave the corresponding 2,4-dichloro derivatives **141** ($\text{X} = \text{X}' = \text{Cl}$) (72BEP769843).

IX. Biological Activity

Biological activity depends on the functional group present in the parent ring system, especially in the pyrimidine nucleus.

A. THIENO[2,3-*d*]PYRIMIDINES

The 2- and 4-alkyl and aryl derivatives showed CNS depressant activity (72USP3654204) as well as analgesic, antiinflammatory, antipyretic, anticholesteremic, and blood-sugar lowering effects [75JAP(K)75/140487; 76JAP76/43796; 77JAP(K)77/46095]; they are also aldose reductase inhibitors (88MI1) and display leishmanicidal (89JPR957), antimicrobial (90PHA216; 91PS223), and antibacterial (88PHA537; 91PHA26) activity. The 4-chloro derivatives exhibited spasmodic (83URP745160) and antiviral activity (87KFZ197). The 4-amino derivatives show antifungal, antiviral, antibacterial, antimicrobial, pesticidal, insecticidal, and acaricidal activity [72GEP(O)2117658; 77GEP(O)2654090; 79SAP78/02648; 81SAP80/00822; 84EUP103114; 86EUP196524; 89YZ464; 90EUP370704; 91EUP411634; 91EUP424125; 91EUP447891; 91JAP(K)03/63266]; they are also anticytokinins (86MI3) and exhibit immunostimulant [91EGP(D)287503] and hypoglycemic (86AF177) activity. The 2-amino derivatives are antidepressant and nootropic agents [85EUP150469; 87JAP(K)62/00427]. The 2,4-diamino derivatives showed antimalarial and antifolate properties (73JMC185, 73JMC188, 73JMC191) and possess antihistaminic (87USP4695575), hypoglycemic, antihypertensive, anticoagulant, and diuretic activity (83EUP82023). The 4-oxo derivatives display analgesic, antiinflammatory, anticholesteremic, sedative, antitussive, hypolipemic, hypnotic, anti-convulsant, diuretic, hypotensive [68MI1; 72GEO(O)2210503; 76IJC-

(B)537; 81JIC982; 83MIP1; 84MI2; 90AF567, 90EUP349239, 90MI2; 91IJC-(B)618], cardiovascular (87JAP62/132884), spasmolytic (90PHA493), fungicidal [75GEP(O)2411274; 81JAP(K)81/08389, 81JAP(K)81/53681, 81JAP(K)8159778], antiviral (80URP677345), antiallergic [77USP4054656; 78BEP859818; 79GEP(O)2746750, 79JMC505; 81EGP(D)152129; 83GEP(O)3231103; 85MI1; 87EUP234557; 88PHA466], immunomodulatory, anticancer (89MIP3; 90JMC1721), and antileukemia activity; they are also inhibitors of adenosine kinase (85JMC423; 89MIP2) and platelet aggregation [82JAP(K)82/77687] and possess affinity for angiotensin II receptors (93MIP1). The 2-oxo derivatives possess diuretic activity [73GEP(O)2323149]. The 2,4-dioxo derivatives are aldose reductase inhibitors, which are used in the treatment of diabetes [90JAP(K)02/252485]; they also show antiulcer [89JAP(K)01/242587], antihypertensive (88JMC1786; 90USP4939137), and antiallergic activity [89JAP(K)01/213284, 89USP4835157]. The 4-mercapto derivatives show insecticidal, acaricidal, and bactericidal (89EUP304155, 89EUP331529; 89MIP1) activity.

B. THIENO[3,2-*d*]PYRIMIDINES

The 2,4-diamino derivatives have been studied over the last three decades as thrombocyte aggregation inhibitors, and as cardiovascular, sedative, and antiinflammatory agents. Owing to the impressive amount of research in this area, the following references are limited to some of the pioneering work [70MI1; 71GEP(O)1940572, 71GEP(O)2003714, 71MI2; 72GEP(O)2032686, 72GEP(O)2032687, 72GEP(O)2058085, 72GEP(O)2058086; 72MI2, 72MI3, 72MI4; 73GEP(O)2137341, 73GEP(O)2215299, 73MI2, 73MI3; 74MI4; 75MI1]. These derivatives also exhibit antitumor activity (86JHC1757).

The 4-amino derivatives are antimicrobial [72GEP(O)2050816; 74MI3], hypoglycemic (86CPB4150), antiviral [91JCS(P1)195], insecticidal and fungicidal [91JAP(K)03/63271] agents, and show antiulcer activity (90EUP404356). The 4-oxo derivatives are antibacterial, fungicidal, and antitrichomonal agents [71GEP(O)1959402; 72GEP(O)-2039663, 72GEP(O)2050814, 72GEP(O)2050815] as well as anticoccidial (88USP4725599) and antiulcer [88JAP(K)63/225383] agents. They serve as hypnotics (68MI1), analgesics, and CNS depressants [91IJC(B)618] as well as purine nucleoside phosphorylase inhibitors and antiprotozoal, cytotoxic, and antileukemia agents (84MI1; 86MI2, 86MI3). In addition, they act as angiotensin II antagonists (92EUP502725, 92MIP1). The 2,4-dioxo derivatives are antihypertensive agents (88JMC1786) and serve as aldose reductase inhibitors in the treatment of diabetes [90JAP(K)02/225485]; they are

also antagonists and alpha adrenergic blocking agents (89USP4835157) and allergy inhibitors [89JAP(K)01/213284].

C. THIENO[3,4-*d*]PYRIMIDINES

The 4-amino derivatives possess analeptic activity (72BEP769843). The 4-oxo derivatives are antibacterial agents (72USP3644357) and phosphorylase inhibitors (86MI2), and they exhibit antiprotozoal, cytotoxic (84MI1), antispasmodic (72BEP769844), and pesticidal (91EUP452002) activity. The 2,4-dioxo derivatives are antiinflammatories, analgesics, and CNS depressants [76JAP(K)7688993]; they are also antihypertensives and vasodilators (87USP4670560; 88JMC1786; 90USP4939137), antagonists and alpha adrenergic blocking agents (89USP4835157), and phosphodiesterase inhibitors (89MI5; 90MI1).

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Cycloadditions and Reactions of Oxa-Aromatics with Nucleophiles

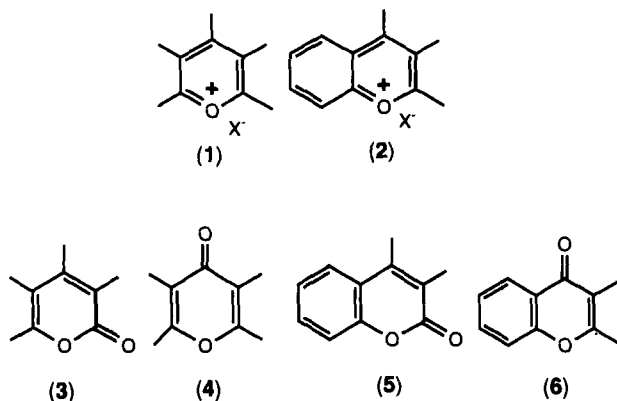
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I. Introduction

Pyrylium salts, pyrone derivatives, and their benzo derivatives show various interesting reactivities and appear in many natural products. Therefore, many organic chemists have an interest in the chemistry of pyrylium salts **1** and **2** and pyrones **3** and **4** (Scheme 1) (82AHC66; 83AHC187). This review is a survey of the literature from 1980 onward, concentrating especially on nucleophilic reactions and carbocyclic annulation reactions that retain the resulting pyran ring. Related benzopyrone derivatives, coumarins (**5**) and chromones (**6**), are also included.

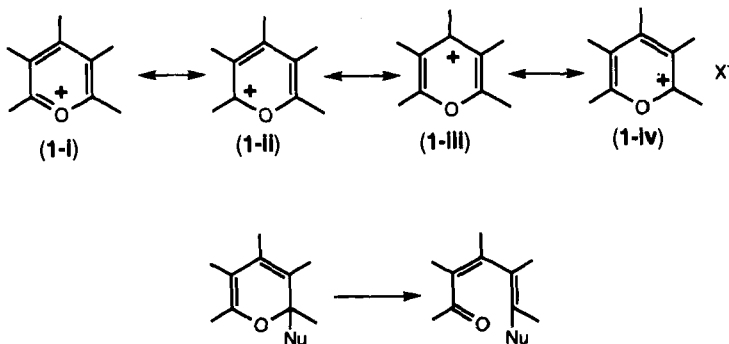


SCHEME 1

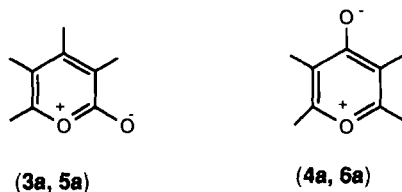
II. Reactions of Pyrylium Salts and Pyrones with Nucleophiles

As indicated by canonical resonance structures **1-i** through **1-iv** of the pyrylium ion (Scheme 2), nucleophilic addition may occur at the 2-, 4-, or 6-position where the positive charge appears. Most reactions occur at the 2- or 6-position (α -positions), then usually proceed further through thermally allowed electrocyclic ring opening of the resulting α -pyran, which is a valence isomer of a 2,4-pentadien-1-one derivative [82AHC66; 83AHC187; 89JCS(P1)683; 91JCS(P1)2725; 92MI1].

Pyrones **3-6** are regarded as synthetically equivalent to oxidopyrylium ions **3a-6a** (Scheme 3) because of the polarizable carbonyl group. Most



SCHEME 2



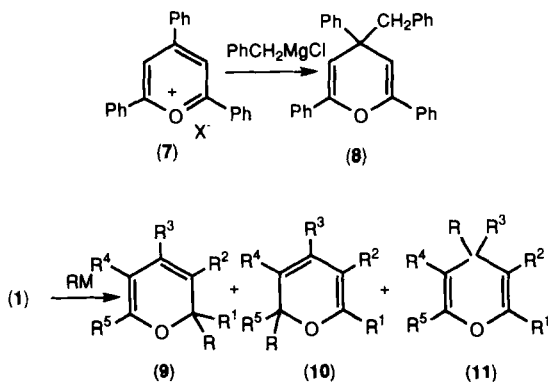
SCHEME 3

nucleophiles attack the 2- and 4-positions, which are more positively charged. The reactions can be separated into 1,2- and 1,4-addition (Michael addition) at the α,β -unsaturated carbonyl moiety.

A. REACTIONS WITH CARBON NUCLEOPHILES

1. Reactions of Pyrylium Salts

a. *Organometallic Reagents* (RLi , $RMgX$, R_2CuLi , $R_3SiCH_2CH=CH_2$, etc.). 2,6-Disubstituted or 2,4,6-trisubstituted pyrylium salts may be attacked at the α - or γ -positions, providing 2*H*- and/or 4*H*-pyrans. The reaction of pyrylium salts with an organometallic reagent RM is an applicable method for the preparation of substituted 2*H*- and 4*H*-pyrans and related compounds. The synthesis of **8** (Scheme 4) is an example (59CB2042; 60AG778). Reaction of the substituted pyrylium ions **1** with RM gives a mixture of two isomeric 2*H*-pyrans, **9** and **10**, together with 4*H*-pyran **11**. 2,6-Disubstituted ions **1** ($R^2 = R^3 = R^4 = H$) provide, generally, 4*H*-pyrans

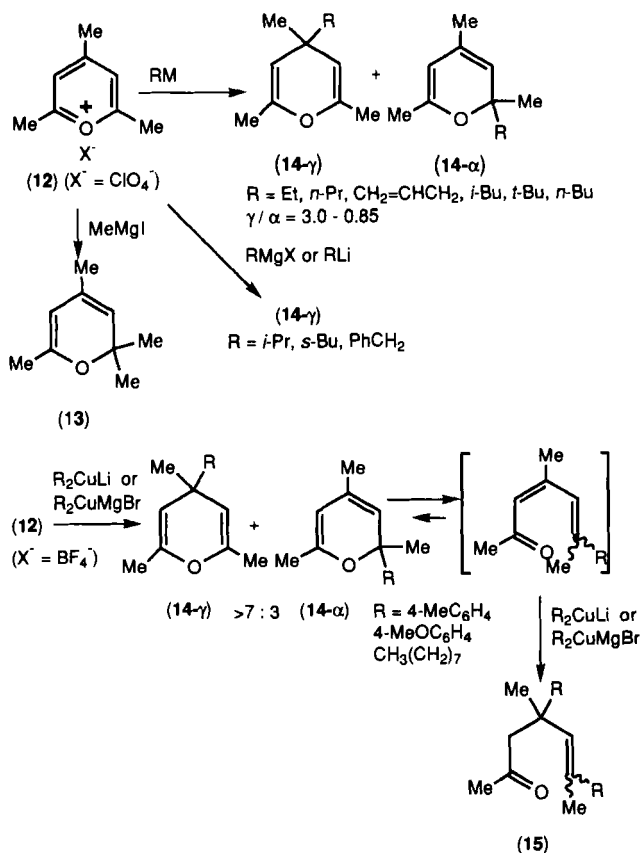


SCHEME 4

11 independently of the nature of the organometallic reagent (64LA183; 72BSF707; 74ZOR1998; 77ZOR1294).

The regioselectivity of the addition of organometallics to 2,4,6-trisubstituted pyrylium ions **1** ($R^2 = R^4 = H$) is mainly determined by the structure of the entering group R . Thus, 2,4,6-trimethylpyrylium perchlorate **12** (Scheme 5) reacts with MeMgI , MeLi , or MeNa exclusively to give 2,2,4,6-tetramethyl-2*H*-pyram **13**, whereas $i\text{-PrMgX}$, $i\text{-PrLi}$, $s\text{-BuMgX}$, and PhCH_2MgCl yield only 4*H*-isomers **14-γ**. Analogous reactions with EtMgX , $n\text{-PrMgX}$, $\text{CH}_2=\text{CHCH}_2\text{MgX}$, $i\text{-BuMgX}$, $t\text{-BuMgX}$, $n\text{-BuLi}$, and $n\text{-BuNa}$ are less regioselective; $\gamma/\alpha = 3.0\text{--}0.85$ [72BSF703, 72CR(C)1849].

On the other hand, cuprates such as R_2CuLi or R_2CuMgBr [$R = 4\text{-MeC}_6\text{H}_4$, $4\text{-MeOC}_6\text{H}_4$, $\text{CH}_3(\text{CH}_2)_7$] react with **12** at the 4-position to give

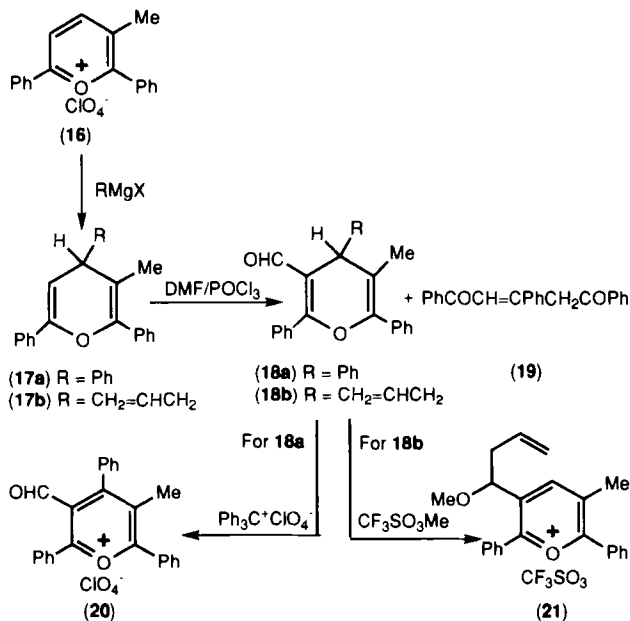


SCHEME 5

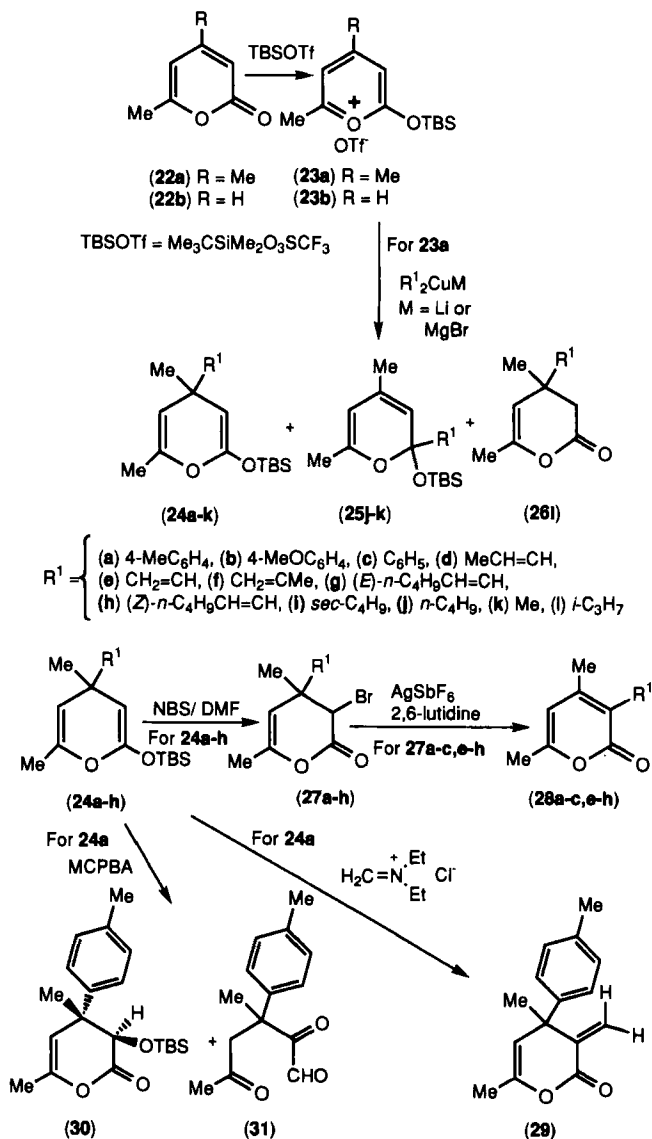
4*H*-pyrans **14-γ** as major products with good regioselectivity (4*H*:2*H* > 7:3) in 75–90% yield. 2*H*-Pyrans **14-α** are in equilibrium with valence isomers, which then react further by 1,4-addition of RM to give **15** (87H1495).

The reaction of 2,6-diphenyl-3-methylpyrylium perchlorate **16** with PhMgBr and CH₂=CHCH₂MgCl gives 72–87% 4*H*-pyrans **17a–b**, followed by formylation with DMF–POCl₃ to give 60–68% of 3-formyl-4*H*-pyrans **18a–b** and 10% of PhCOCH=CPhCH₂COPh (**19**). As shown in Scheme 6, **18a** reacts with Ph₃C⁺ClO₄[−] in dry MeNO₂ to give pyrylium salt **20** in 86% yield (90KGS603), while treating **18b** with CF₃SO₃Me in C₂H₄Cl₂ gives the rearranged pyrylium salt **21** in 76% yield.

As shown in Scheme 7, silylation of 4,6-dimethyl- (**22a**) and 6-methyl-2-pyrone (**22b**) with Me₃CMe₂SiO₃SCF₃ (TBSOTf) affords 2-(silyloxy)pyrylium triflates **23a–b** quantitatively (89JOC1931). Reactions of **23a** with organocuprates give various pyran derivatives **24a–k**, **25j–k**, and **26l** (87TL6305). In most reactions (aryl, alkenyl, and secondary alkyl cuprates), the substituent R¹ is introduced regioselectively at the 4-position to produce **24a–i** in 28–71% yield. Primary alkyl or methyl cuprates give mixtures of **24j–k** and **25j–k** in 53–70% yield. The lithium diorganocuprates (R₂¹CuLi)



SCHEME 6



SCHEME 7

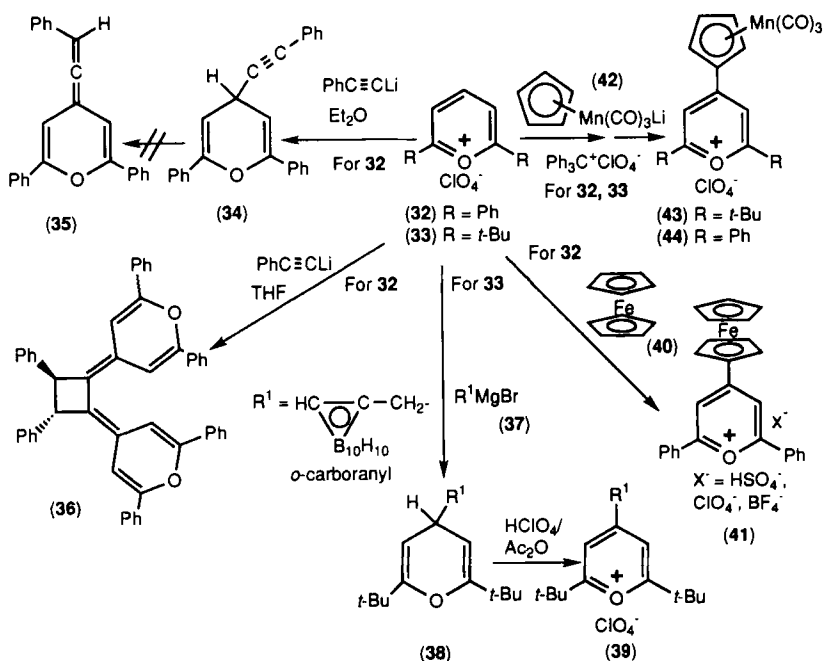
react more efficiently than the cuprates (R^1_2CuMgX) prepared from Grignard reagents and the olefin geometry is retained. Hydrolyzed product **26l** is obtained in the reaction of the diisopropylcuprate prepared from a Grignard reagent.

Treatment of **24a-h** with *N*-bromosuccinimide in DMF gives mainly *trans*-bromodihydropyrans **27a-h** (*trans/cis* = 74/26–89/11) in 56–92% yield.

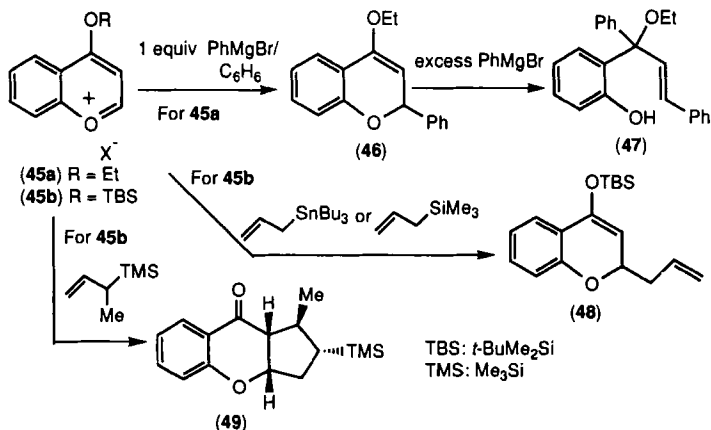
Debromination of 4-aryl- and 4-alkenyl-3-bromo-4,6-dimethyl-3,4-dihydro-2-pyrones **27a-c** and **27e-h** with AgSbF₆ in CH₂Cl₂ or ClCH₂CH₂Cl induces rearrangement of the aryl or alkenyl group at the 3-position to afford the respective 3-substituted 2-pyrones **28a-c** and **28e-h** in high yield (88TL3825; 89JOC1935).

Reaction of **24a** with CH₂=N⁺Et₂Cl⁻ gives **29** in 63% yield. Oxidation of **24a** with *m*-chloroperbenzoic acid (MCPBA) gives 33% of **30** of 19% of MeCOCH₂Me(4-MeC₆H₄)COCHO **31** (87TL6305).

The reaction of 2,6-diphenylpyrylium perchlorate **32** with PhC≡CLi in refluxing Et₂O gives pyran **34**, not the previously assigned structure **35** (Scheme 8) (82TL1747). In contrast, the reaction of **32** with PhC≡CLi in THF at room temperature gives 72% of cyclobutane **36**. Treating 2,6-di-*t*-butylpyrylium perchlorate **33** with R¹CH₂MgBr **37** (R¹ = *o*-carboranyl) affords **38**, which gives 81% of **39** on treatment with HClO₄ in Ac₂O (80KGS189, 80MI2). Refluxing **32** with ferrocene **40** in Ac₂O gives 81–2% of **41** (80ZOB563). Treating pyrylium salts **32** and **33** with **42** gives pyrans



SCHEME 8



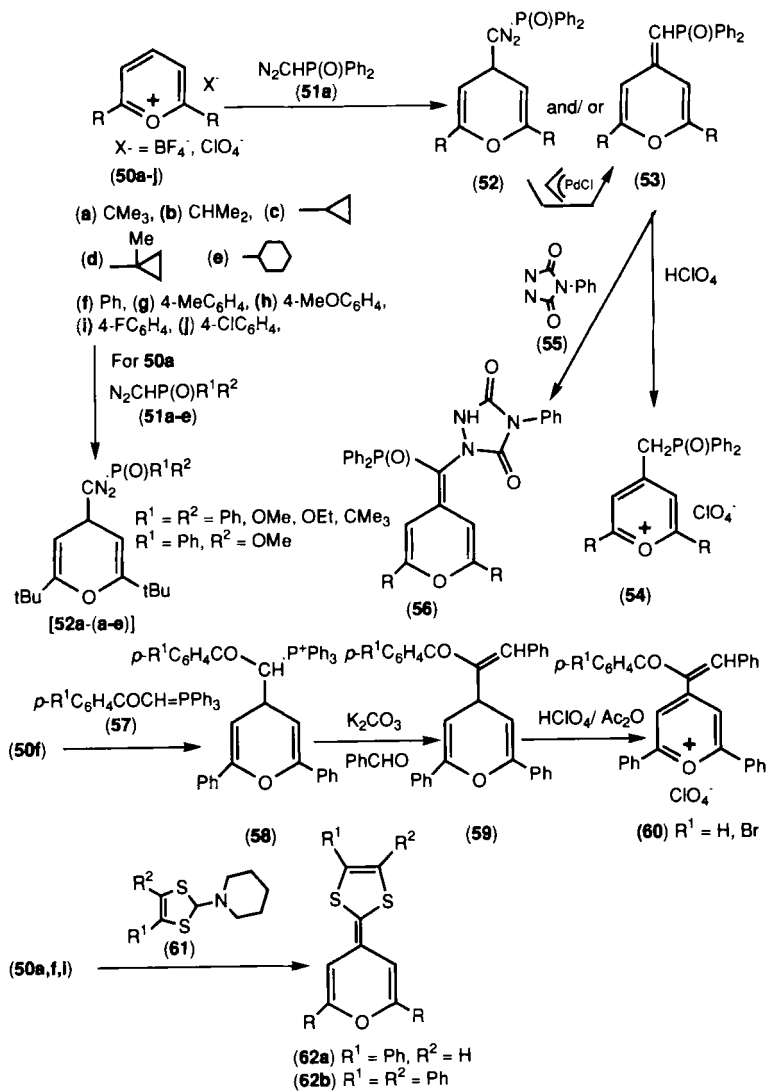
SCHEME 9

that, on treatment with $\text{Ph}_3\text{C}^+\text{ClO}_4^-$, give 98% of **43** and 96% of **44**, respectively (85KGS593).

Treatment of 4-ethoxy-1-benzopyrylium salt **45a** with 1 equivalent of PhMgBr in C_6H_6 gives chromene **46** (32%), whereas treatment of **45a** with excess PhMgBr gives phenol derivative **47** (62%) (Scheme 9) (81ZOR880). Reaction of 4-*t*-butyldimethylsilyloxy-1-benzopyrylium salt **45b** with allylstannane gives the corresponding allylated derivative **48** (85%) more smoothly than does allylsilane (90CL1725; 91JOC2058). A similar reaction with 3-trimethylsilyl-1-butene affords an unexpected five-membered ring adduct **49** in 87% yield.

b. Active Methyl(ene) Reagents Stabilized by a Carbonyl Group or Heteroatom. Reaction of pyrylium tetrafluoroborate **50a** ($\text{R} = \text{CMe}_3$) with $\text{N}_2\text{CHP}(\text{O})\text{R}^1\text{R}^2$ **51a–e** ($\text{R}^1 = \text{R}^2 = \text{Ph}$, OMe , OEt , CMe_3 ; $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{OMe}$) gives pyrans **52a(a–e)**, as shown in Scheme 10 (84CB2233). Similarly, reactions of **50a–j** with $\text{N}_2\text{CHP}(\text{O})\text{Ph}_2$ (**51a**) give mixtures of **52f,i,j** and **53f,i,j** or only one of these products, **52a,c,d,g,h** or **53b,e**. Treating **52a,d,f–j** with μ -allylpalladium chloride gives **53a,d,f–j**, which are characterized by protonation with HClO_4 to give **54**. Reaction of **53** with 4-phenyl-1,2,4-triazoline-3,5-dione **55** affords urazoles **56**.

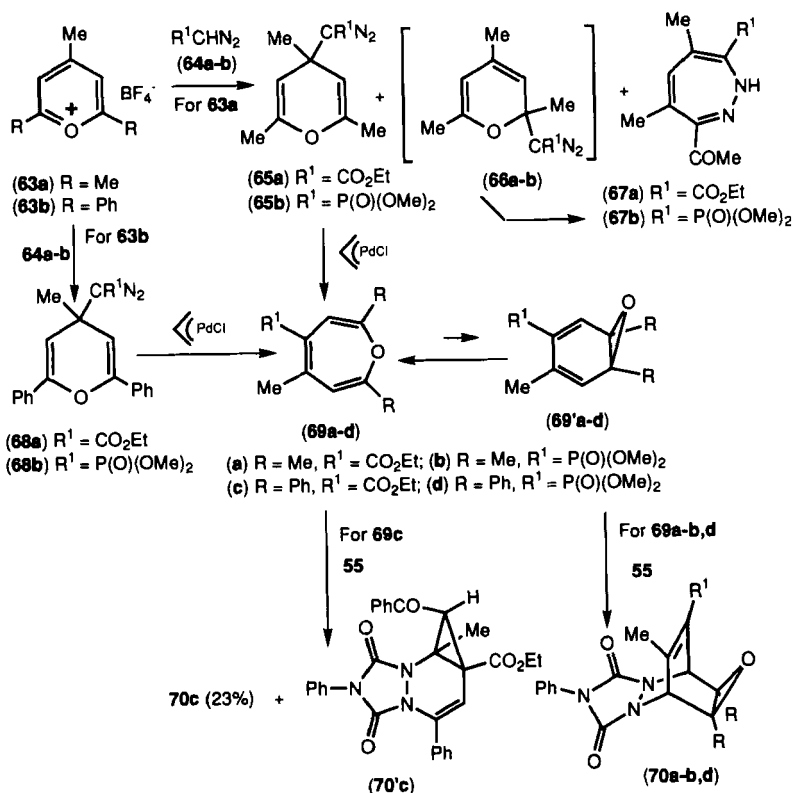
Reaction of 4- $\text{R}^1\text{C}_6\text{H}_4\text{COCH}=\text{PPh}_3$ **57** ($\text{R}^1 = \text{H}$, Br) with **50f** gives 63–76% of **58** (80ZOB1473). Treatment of **58** with 10% aqueous K_2CO_3 followed by reaction with PhCHO gives 58–68% of **59**, which gives 78–81% of **60** on treatment with 70% HClO_4 in Ac_2O . When condensed in acetonitrile at 70°C with 2-piperidino-1,3-dithiols **61** ($\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$, Ph),



SCHEME 10

pyrylium salts **50a,f,i** form 2-(pyran-4-ylidene)-1,3-dithiols **62a-b** ($\text{R} = \text{Me}_3\text{C, Ph, 4-FC}_6\text{H}_4$) in 92–94% yield (85JHC1179).

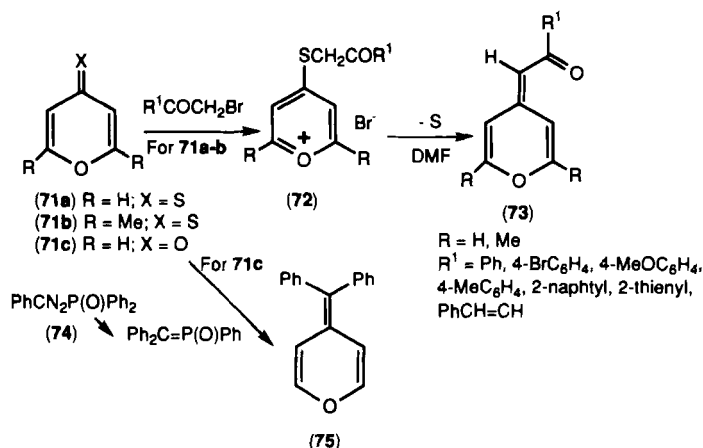
As shown in Scheme 11, reaction of 2,4,6-trimethylpyrylium tetrafluoroborate **63a** with stabilized diazoalkane R^1CHN_2 (**64a-b**) [$\text{R}^1 = \text{CO}_2\text{Et}$,



SCHEME 11

P(O)(OMe)₂] gives the pyrans **65a–b** and the diazepines **67a–b**. Diazepines **67a–b** are formed by spontaneous isomerization of the intermediate 2-(diazomethyl)-2*H*-pyrans **66a–b** (87JOC3851). In contrast, the analogous reactions of 4-methyl-2,6-diphenylpyrylium tetrafluoroborate **63b** with **64a–b** give only **68a–b**. The allylpalladium chloride-catalyzed decomposition of **65a–b** and **68a–b** in benzene solution gives 92–98% of oxepines **69a–b,d**. Oxepines **69a–b,d** react with triazolidinedione **55** to form the Diels–Alder adducts **70a–b,d** (83–89%), which are derived from the valence tautomeric benzene oxides. The corresponding reaction of **69c** with **55** under otherwise identical conditions proceeds differently in that an isomer with structure **70'c** (66%) is formed along with **70c** (23%).

Alkylation of pyrrhione **71a–b** with arenyl bromomethyl ketones R¹COCH₂Br (R¹ = Ph, 4-BrC₆H₄, 4-MeOC₆H₄, 4-MeC₆H₄, 2-naphthyl, 2-thienyl, PhCH=CH) gives pyrylium bromides **72** in 60–95% yields (Scheme

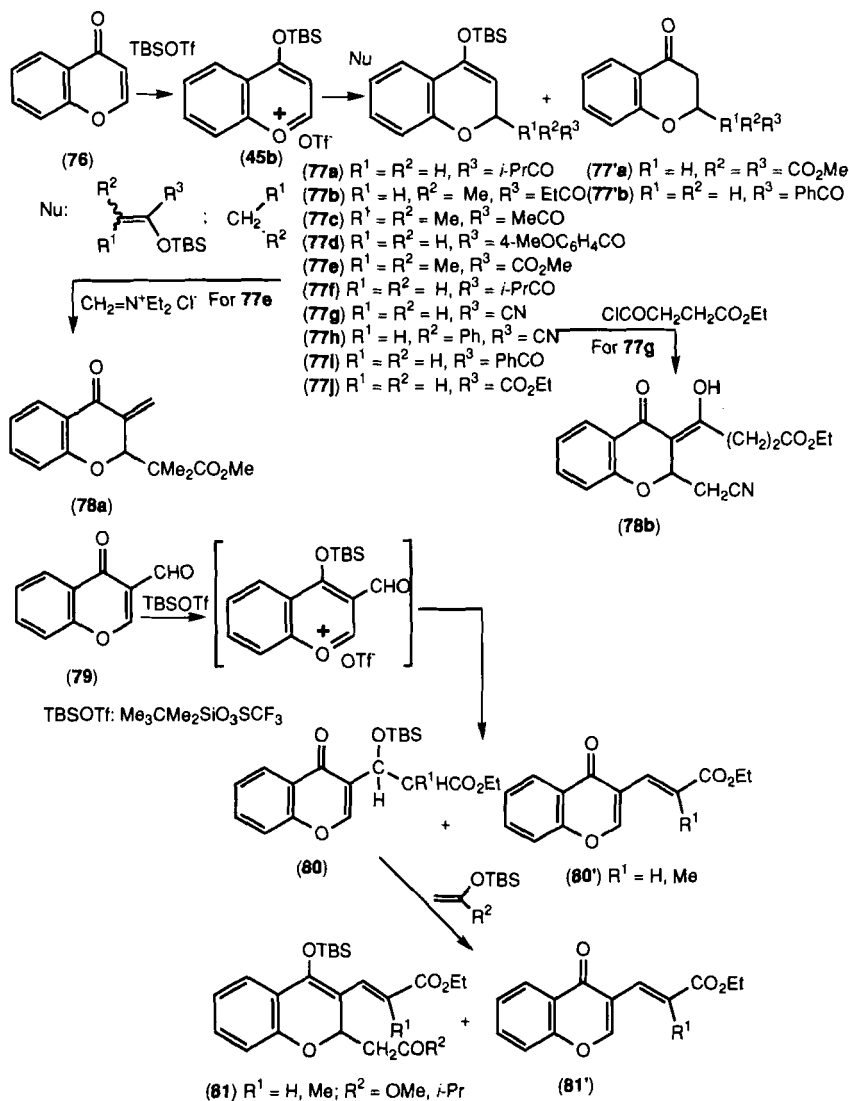


SCHEME 12

12) (86H2817). Sulfide contraction and desulfurization of **72** in DMF gives 8–57% of vinylogous pyrones **73**. Phosphene $Ph_2C=P(O)Ph$, generated thermally or photochemically from diazo compound **74**, undergoes olefination with 4-pyrone **71c** to yield 4-(diphenylmethylene)pyran **75** [85ZN(B)67].

When *t*-butyldimethylsilyloxybenzopyrylium salt **45b** is prepared *in situ* from chromone **76** and TBSOTf, **45b** reacts in the presence of two equivalents of 2,6-lutidine with enol silyl ethers, ketone silyl acetals, and active methylene compounds as a nucleophile (Nu) to give 2-substituted 4-*t*-butyldimethylsilyloxybenzopyrans **77a–j** (Scheme 13). In the presence of 1 equivalent of 2,6-lutidine, the corresponding desilylated ketones **77'a–b** (80–82%) were obtained (87TL6355). When treated with $CH_2=N^+(Et)_2Cl^-$ and $ClCOCH_2CH_2CO_2Et$, **77e,g** give chromanones **78a** (74%) and **78b** (66%). When 3-formylchromone **79** is treated with $R^1CH_2CO_2Et$, TBSOTf, and 2 equivalents of 2,6-lutidine, it gives the addition products **80** (89–96%) and **80'** (6–8%) (88H1599); **80** then reacts with TBSOTf and $CH_2=C(OSiMe_2CMe_3)R^2$ to give **81** (62–74%) and **81'** (18–37%).

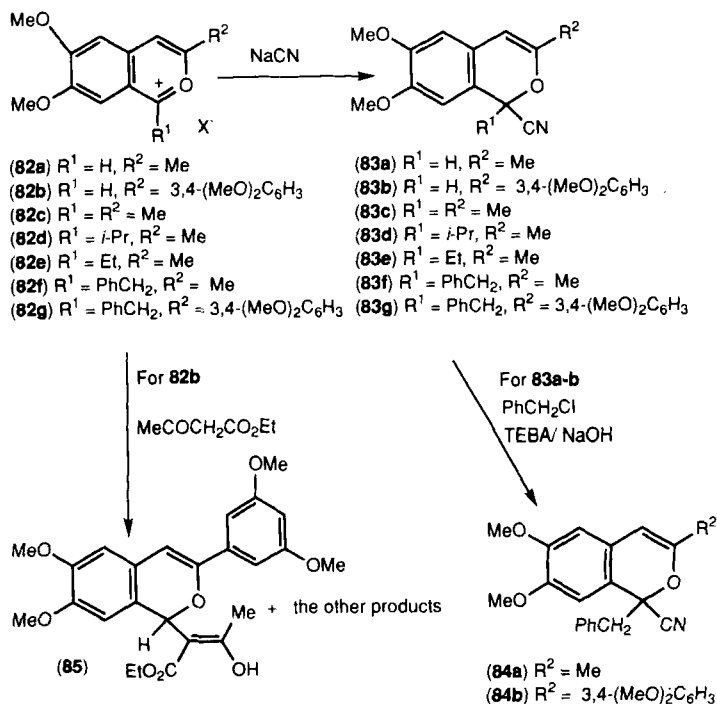
As Scheme 14 shows, nucleophilic addition of cyanide anion to 2-benzopyrylium salts **82a–g** gives 55–80% of cyanoisochromenes **83a–g**, which are oxygen analogs of Reissert compounds (87T409). Cyanoisochromenes **83a–b** are alkylated with $PhCH_2Cl$ under phase-transfer conditions (triethylbenzylammonium chloride, TEBA) to give **84a–b** in 80 and 90% yields, respectively. Reaction of benzopyrylium salts **82b** with $MeCOCH_2CO_2Et$ gives isochromene **85** together with other products (90KGS315).



SCHEME 13

2. Reactions of Pyrone Derivatives

Although pyrone derivatives are a type of α,β -unsaturated carbonyl compound, their reactivity to nucleophiles is greatly decreased owing to the inherent resonance stabilization of the pyrone ring and the conjugation of

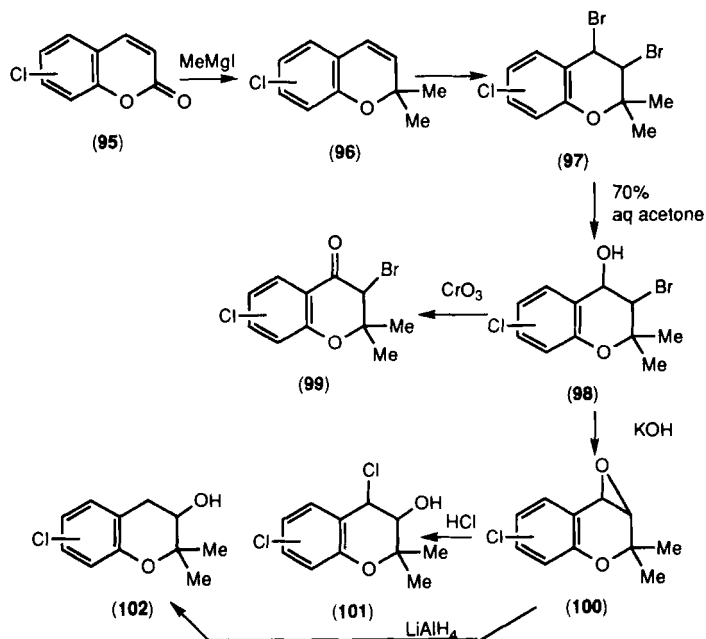


SCHEME 14

enol ether moiety. However, some pyrone derivatives undergo the same nucleophilic reactions as pyrylium salts by means of intermolecular activation with acidic reagents (Lewis acid) or intramolecular activation with an electron-withdrawing group.

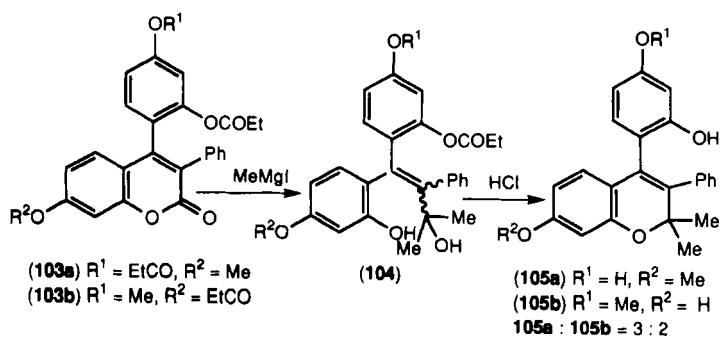
In most reactions of 2-pyrone, alkyl or aryl Grignard halides have been used. The best results have been achieved for 4,6-disubstituted 2-pyrone because of the general stability of 2,2,4,6-tetrasubstituted 2H-pyrans. Thus, 4,6-dimethyl-2-pyrone **86a** reacts with MeMgI via intermediate **87a** to give 2,2,4,6-tetramethyl-2H-pyran **88a** accompanied by its isomer **89a**. (See Scheme 15.) Similarly, 2,2,4,6-tetraphenyl-2H-pyran **88b** was obtained from 4,6-diphenyl-2-pyrone **86b** and PhMgBr by dehydration of intermediate **87b** (83AHC219).

a. *Nucleophilic 1,2-Addition to the Carbonyl Groups.* Reaction of 4-methyl-2-pyrone **90** with MeMgI (Scheme 16) gives dihydropyranol **91a** (65%) and a ring-opening form (ketol) **93a** (6%) along with dehydrated

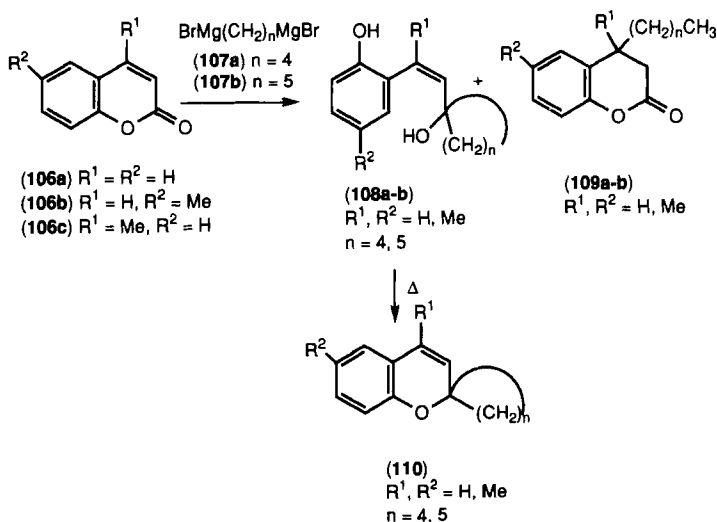


SCHEME 17

of **106a** with **107a** gives 49% of **108a** ($R^1 = R^2 = H$, $n = 4$) and 30% of **109a**, while the reaction with **107b** gives 20% of **108b** ($R^1 = R^2 = H$, $n = 5$) and 38% of **109b**. Dehydration of **108** under distillation affords the spiro compounds **110** in 15–60% yield.



SCHEME 18

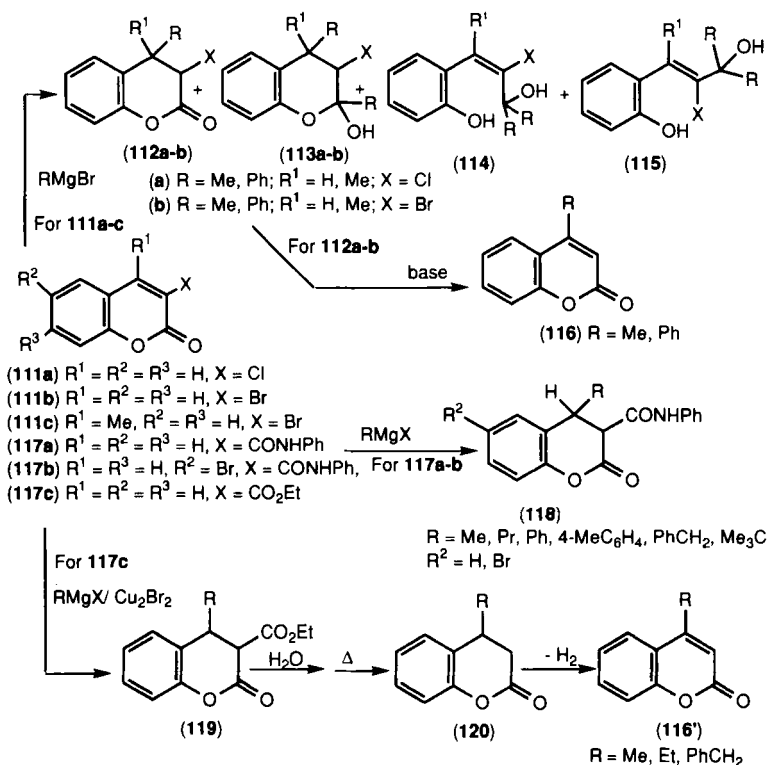


SCHEME 19

b. *Nucleophilic 1,4-Addition to the α,β -Unsaturated Carbonyl Group.*

The reaction of coumarins with organometallic compounds via 1,4-addition (Michael type reaction) is a very well-known synthetic method for 2*H*-1-benzopyrans. Grignard reagents react with 3-chlorocoumarin **111a**, 3-bromocoumarin **111b**, and 3-bromo-4-methylcoumarin **111c** leading to dihydrocoumarins **112**, chromen-2-ols **113**, and the open-chain compounds **114** and **115** (Scheme 20) [91JCS(P1)203]. The nature and the ratio of products in the final mixture depend on the solvent and the organometallic reagent. The 1,4-addition process is favored when the reactions are carried out in ether solvents (THF or diethyl ether) and with increasingly bulky groups *R*; the resulting 4-alkyl-3-halogeno-3,4-dihydrocoumarins **112a** (*R* = Me, $\text{R}^1 = \text{H}$, X = Cl) and **112b** (*R* = Me, $\text{R}^1 = \text{H}$, X = Br) are obtained as a mixture of *cis* (80–90%) and *trans* (20–10%) isomers. In case of phenylmagnesium bromide, 3-chlorocoumarin (**111a**) yields 3-chloro-3,4-dihydro-2,4-diphenyl-2*H*-1-benzopyran-2-ol **113a** (*R* = Ph, $\text{R}^1 = \text{H}$, X = Cl). Reaction of **111a** with lithium dimethylcuprate yields **112a** (65%) as a mixture of *cis* (60%) and *trans* (40%) isomers. The isomeric mixture of 4-alkyl-3-halogeno-3,4-dihydrocoumarins **112a-b** is transformed into 4-alkylcoumarins **116** by base-promoted dehydrohalogenation (pyridine at 50°C or Ac_2O -AcONa at reflux temperature). The major isomer (*cis*) of the 3-bromo derivatives **112b** (*cis*) is easily dehydrated in pyridine at 50°C, whereas the minor component **112b** (*trans*) is recovered unchanged.

Scheme 20 also show that reaction of carbamoylcoumarins **117a-b** with Grignard reagents RMgX (*R* = Me, X = I; *R* = Ph, Pr, 4-MeC₆H₄, X =

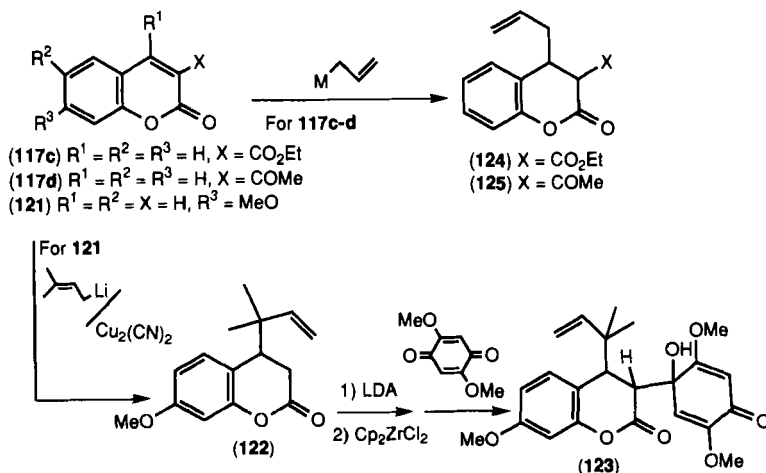


SCHEME 20

Br; R = PhCH₂, CMe₃, X = Cl) gives dihydrocoumarins **118** (82MI1). The Grignard addition of alkylmagnesium halides to 3-ethoxycarbonylcoumarin **117c** in the presence of Cu₂Br₂ gives **119** (75–90%) followed by hydrolysis in aqueous ethanolic NaOH and decarboxylation with HCl to afford dihydrocoumarins **120** [88IJC(B)272]. Dehydrogenation of **120** with 10% Pd–C in Ph₂O affords 4-alkylcoumarins **116'** in 65–70% yield.

Reaction of 7-methoxycoumarins **121** in THF with 1.6 equivalents of the Gilman reagent prepared from phenyllithium and cuprous cyanide gives the conjugate addition product **122** in 91% yield (94TL663). (See Scheme 21.) Treatment of **122** with 1 equivalent of lithium diisopropylamide in THF at –78°C generates the corresponding lithium enolate. When the lithium enolate of **122** is converted to the less electron-rich zirconium enolate by reaction with 1 equivalent of Cp₂ZrCl₂ prior to the reaction with 2,5-dimethoxy-1,4-benzoquinone, two diastereomeric aldol adducts **123** (ratio 1.3:1) are obtained in 82% yield.

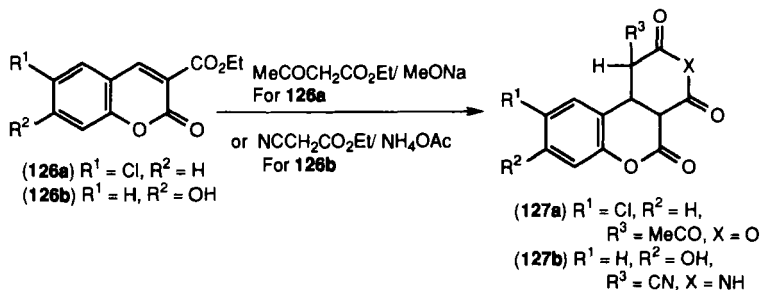
Conjugate addition to 3-ethoxycarbonylcoumarin (**117c**) using lithium diallylcuprate affords the 1,4-adduct **124** in 83% yield while the application



SCHEME 21

of this method to 3-acetyl derivative **117d** gives only the decomposed product (83TL1909; 86JOC1745). An alternative allylation procedure (acid-catalyzed addition of trimethylallylsilane) is effective for both coumarins, giving the 1,4-adducts **124** (49%) and **125** (79%), respectively. The conjugate allylation of the coumarins **117c-d** using trimethylallylsilane and fluoride catalysis gives the 1,4-adducts **124** and **125** in 91 and 22% yields, respectively. The allylic carbanion generated by treatment of $CH_2=CHCH_2SiMe_3$ with F^- undergoes highly chemoselective conjugated addition to a series of Michael acceptors.

Reaction of 6-chloro-3-ethoxycarbonylcoumarin **126a** with $MeCOCH_2CO_2Et$ at room temperature in the presence of $MeONa$ (Scheme 22) gives the Michael adduct, which is cyclized into anhydride **127a** [79IJC(B)460]. Heating a mixture of **126b**, $NCCH_2CO_2Et$, and NH_4OAc catalyst at $170^\circ C$ results in **127b** (83RRC641).



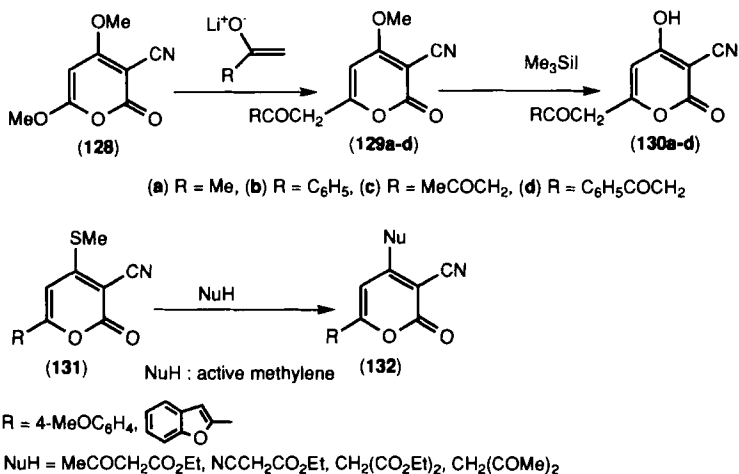
SCHEME 22

Reaction of 4,6-dimethoxy-2-pyrone **128** with lithium enolates gives 6-substituted 2-pyrone **129a-d** (52–82%), followed by demethylation with Me_3SiI to give 4-hydroxy derivatives **130a-d** (52–65%) (Scheme 23) (82TL1971). The methylthio group on 6-aryl- and 6-styryl-3-cyano-4-methylthio-2*H*-pyran-2-one derivatives **131** reacts readily with nucleophiles such as active methylene compounds to yield the corresponding displacement products **132** in good yields via an addition-elimination process [84CPB3384; 90IJC(B)624].

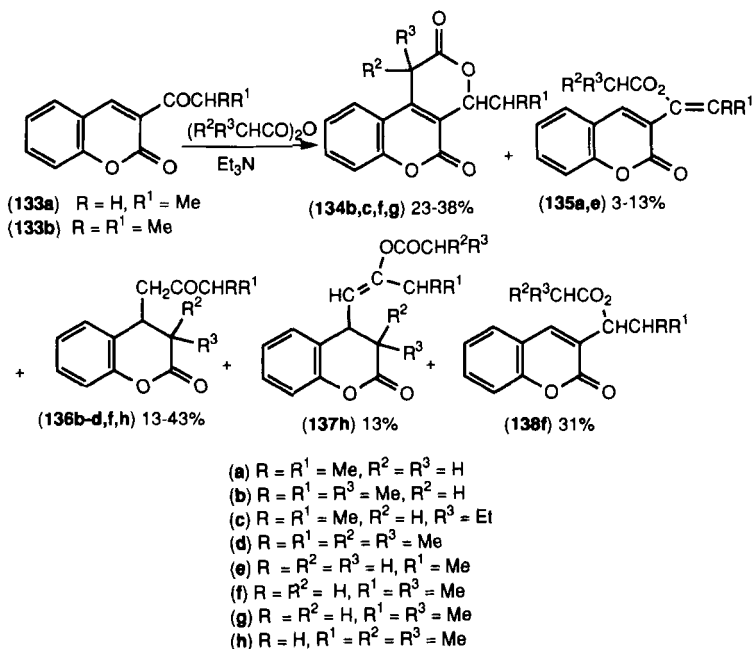
As shown in Scheme 24, reaction of 3-propionyl- and 3-isobutyryl-2*H*-1-benzopyran-2-ones **133a-b** with $(\text{R}^2\text{R}^3\text{CHCO})_2\text{O}$ ($\text{R}^2 = \text{H}$, $\text{R}^3 = \text{H}$, Me, Et; $\text{R}^2 = \text{R}^3 = \text{Me}$) in the presence of Et_3N affords bislactones **134b,c,f,g**, *O*-acylating products **135a,e**, and several other products (**136–138**) containing the ring-transformed compounds (91LA1279).

Arylation of 4-hydroxycoumarin derivatives **139a-d** by various substituted aryllead triacetates **141a-f** gives a range of 3-aryl-4-hydroxycoumarins **142** in 40–97% yield (89TL1539). The same reaction of 3-hydroxycoumarin derivatives (**140a-b**) gives **143** in 56–92% yield [90JCS(P1)2851]. (See Scheme 25.) The direct arylation of **139a** with triarylbismuth(V) reagents **141i-j** gives **142** in good yield (88T6387). The organometallic reagents behave as aryl cation equivalents, thus permitting selective arylation of the activated position in **139** and **140**.

These are not nucleophilic reactions, but they offer a convenient method for arylation at C_3 or C_4 of hydroxycoumarins **139** and **140** under mild conditions. The arylation of **140a-b** with **141a-c** and **141f-h** affords **143** in



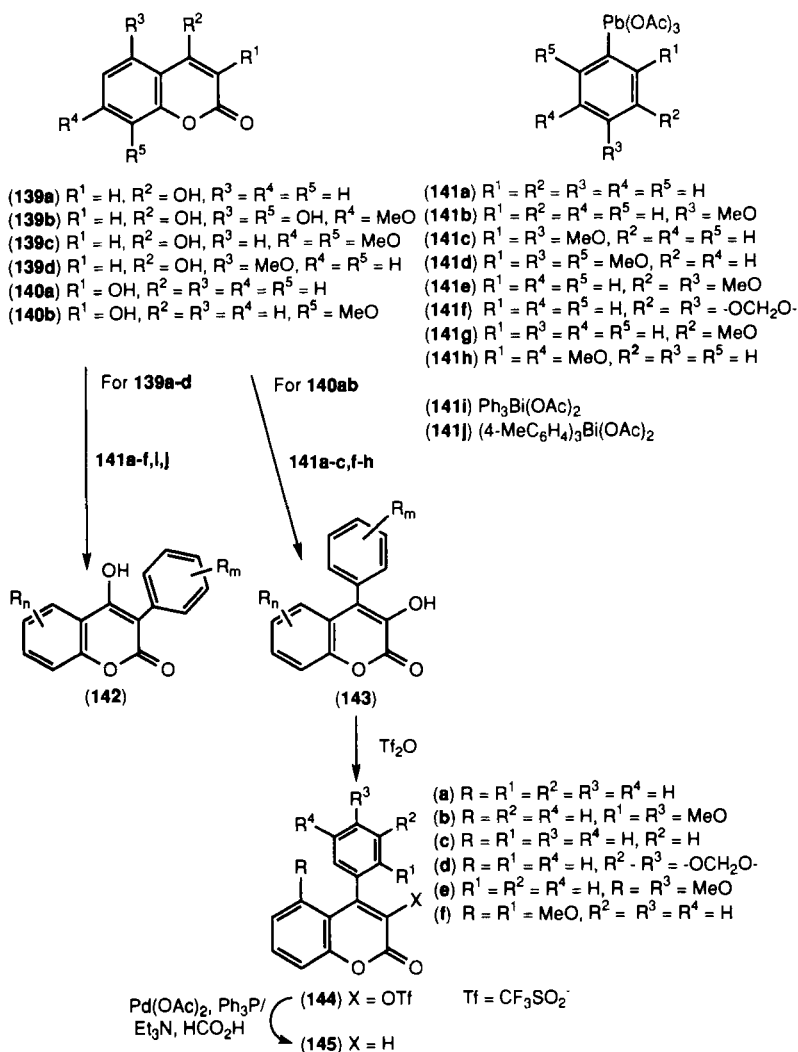
SCHEME 23



SCHEME 24

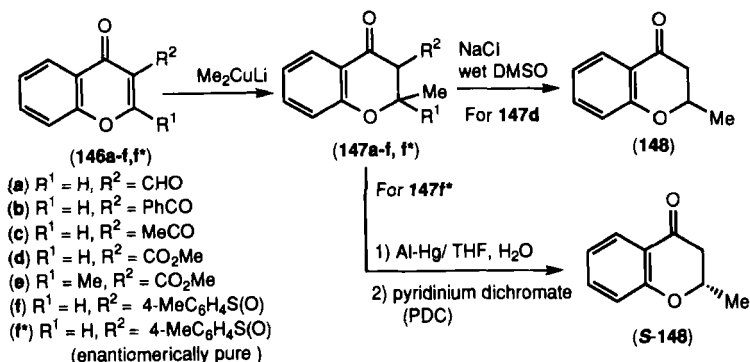
56–92% yield. Triflation of 3-hydroxycoumarins **143** with trifluoromethanesulfonic anhydride, followed by Pd-catalyzed reduction [$Pd(OAc)_2$, Ph_3P , Et_3N , and HCO_2H] of **144** gives neoflavonoids or 4-aryl coumarins **145** [90JCS(P1)2851].

Chromones (4-oxo-4H-1-benzopyrans) activated by electron-withdrawing groups attached to C-3 undergo efficient 1,4-addition of a cuprate reagent to afford 2,3-disubstituted chroman-4-ones. Thus, as Scheme 26 shows, chromones **146a–e** activated by carbonyl substituents at C-3 are transformed into 2-methyl-4-chromanes **147a–e** by treatment with lithium dimethylcuprate (84TL4299). Demethoxycarboxylation of **147d** with $NaCl$ in aqueous Me_2SO gives **148**, which is isolated as the 2,4-dinitrophenylhydrazone in 77% yield (90T3029). The conjugate addition of Me_2CuLi to chromone **146f** proceeds with at least 90% diastereoselectivity using a chiral sulfinyl auxiliary. The products **147f*** from (*S*)-**146f*** can be converted to chiral methylchromanone (*S*)-**148** in 65% yield via three steps (86CC1592).



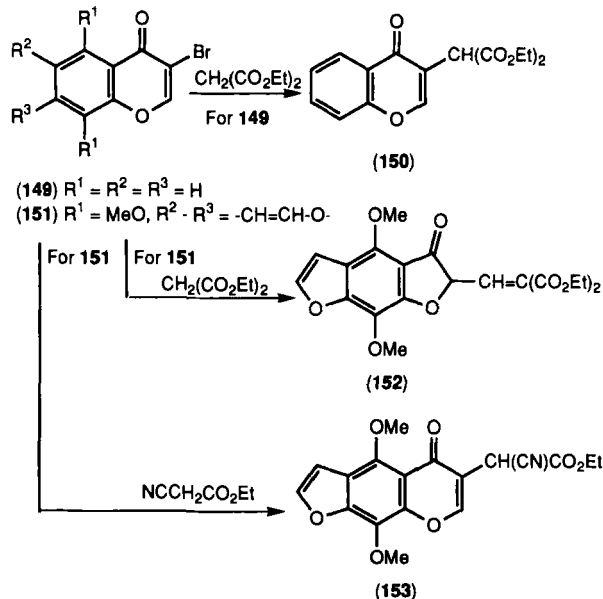
SCHEME 25

Scheme 27 shows that 3-bromochromone **149** reacts with $CH_2(CO_2Et)_2$ to give **150**, while $CH_2(CO_2Et)_2$ reacts with **151** to give a ring-contracted product, furobenzofuranone **152** (92TL997). However, **151** reacts with EtO_2CCH_2CN to give **153**.



SCHEME 26

c. *Transition-Metal-Catalyzed Carbon-Carbon Bond Formations (Coupling Reactions).* Palladium-catalyzed coupling reactions of pyrone derivatives with organometallic reagents are also used to introduce substituents into the heterocyclic ring. Thus, the $(\text{PPh}_3)_4\text{Pd}$ -catalyzed coupling reaction



SCHEME 27

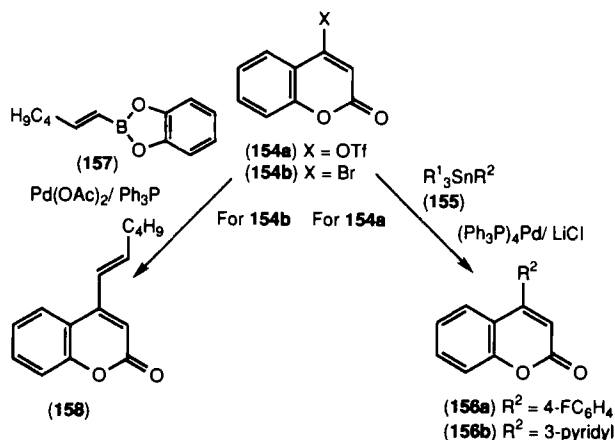
of coumarin **154a** with $(R^1)_3R^2Sn$ **155** ($R^1 = Bu$, $R^2 = 4-FC_6H_4$; $R^1 = Me$, $R^2 = 3\text{-pyridyl}$) in dioxane in the presence of LiCl gives 76–89% of coumarins **156a–b**, respectively (Scheme 28) (88SC1919). Cross-coupling of 4-bromocoumarin **154b** with 2-[(*E*)-1-hexenyl]-1,3,2-benzodioxaboroles **157** in the presence of 3 mol% of $Pd(OAc)_2$, PPh_3 , and 2 equivalents of Na_2CO_3 or K_2CO_3 in alcohol gives **158** in high yield, while retaining the original configuration of the double bonds in the 1-alkenylboronates (89BCJ3892).

Arylation of 8-methyl-4*H*-1-benzopyran-4-ones **159a–b** by C_6H_6 in the presence of $Pd(OAc)_2$ in AcOH affords flavones **160a–b** in 16–24% yield (94MI1). (See Scheme 29.) Cross-coupling reactions of 3-iodochromone **159c** with **161a–e** catalyzed by $(PPh_3)_4Pd$ give idoflavones **162a–e** in high yield (89CPB529). Thiophene-2-boronic acid **161f** is also coupled with **159c** under the same conditions to afford **162f** in 70% yield.

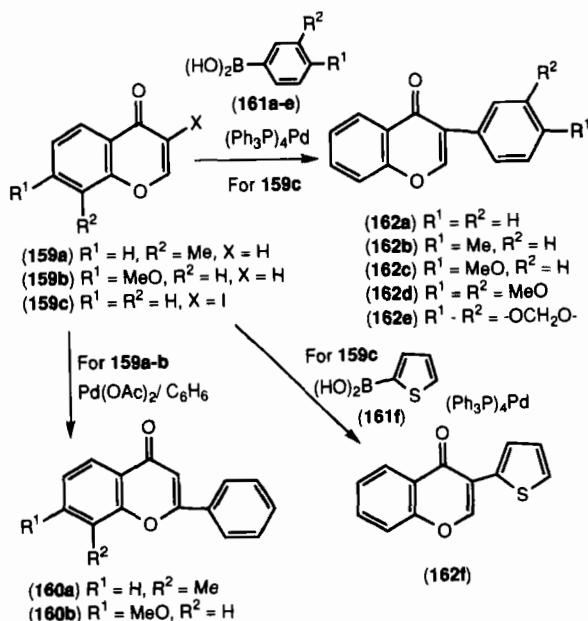
As shown in Scheme 30, reaction of 3-cuprio-2-pyrone **163** with various alkenyl bromides in ether at $-78^\circ C$ gives the corresponding coupling products **164a–c** (85JOC5041). The cupriopyrone **163** can be used to prepare 3-sulfur-substituted 2-pyrones **165** in 45–82%. Oxidation of **165a** with *m*-chloroperbenzoic acid (MCPBA) gives **165b** and **165c**.

B. REACTIONS WITH NITROGEN NUCLEOPHILES

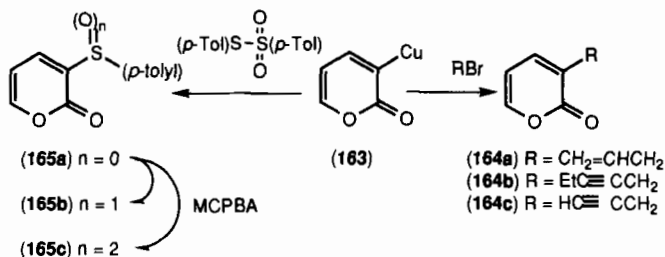
Most reactions of nitrogen nucleophiles with pyrylium salts occur at the 2- or 6-position to give 2*H*-pyran derivatives, which isomerize spontaneously



SCHEME 28



SCHEME 29

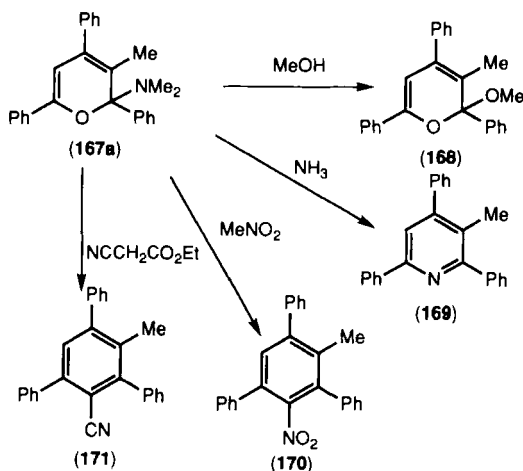
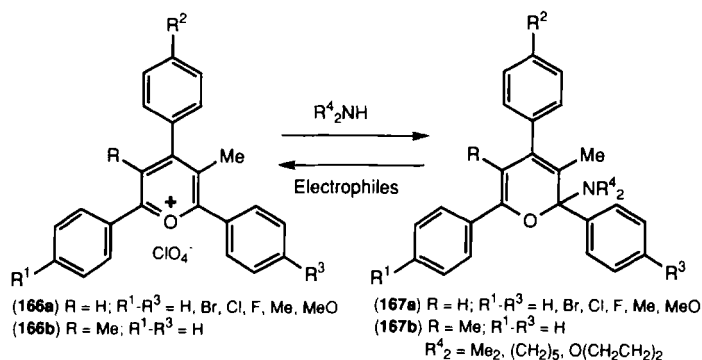


SCHEME 30

under electrocyclic ring opening to vinylogous amides, according to the nature of their substituents. An excess of primary amines usually converts the pyrylium salts to pyridinium salts. So far, 2*H*-pyran derivatives have been successfully isolated only with pyrylium salts possessing certain substituent patterns (82AHC47).

1. Reactions of Pyrylium Salts

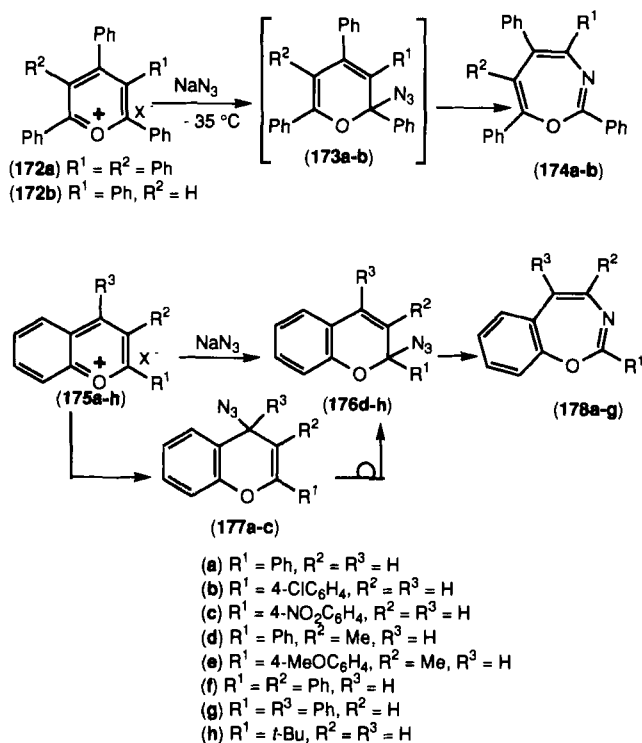
As Scheme 31 shows, tetra- and pentasubstituted pyrylium salts **166a-b** react regiospecifically with R_2^1NH [$R_2^1 = Me_2$, $R_2^1 = (CH_2)_5$, $O(CH_2CH_2)_2$]



SCHEME 31

to give 2H-pyran amines **167** (82ZC282; 84JPR657). The amines **167a–b** react with electrophiles to regenerate **166a–b**. Furthermore, **167a** reacts with refluxing MeOH to give **168** and with NH₃ to give 3-methyl-2,4,6-triphenylpyridine (**169**). Amine **167a** also reacts with MeNO₂ and with EtO₂CCH₂CN to give pentasubstituted benzene derivatives **170** and **171**, respectively.

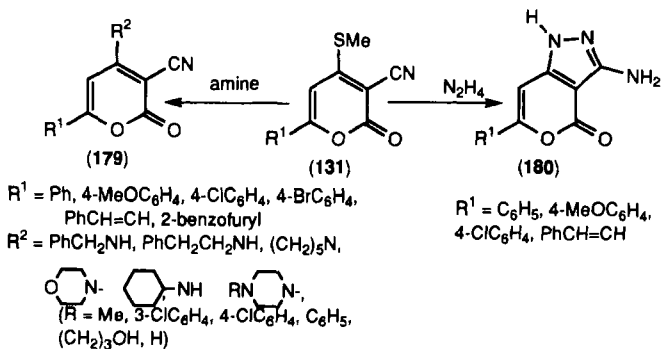
Reaction of pyrylium salts **172a–b** with NaN₃ at –35°C in CH₃CN gives unstable azidopyrans **173a–b**, which rearrange at room temperature to 1,3-oxazepines **174a–b** in 70–80% yield (84T3559). (See Scheme 32.) Chromylium salts **175a–h** are treated with NaN₃ to give the chromenes **176d–h** and **177a–c** (84T3567), and **176** and **177** undergo thermal rearrangement to the benzoxazepines **178a–g** (70–85%).



SCHEME 32

2. Reactions of Pyrone Derivatives

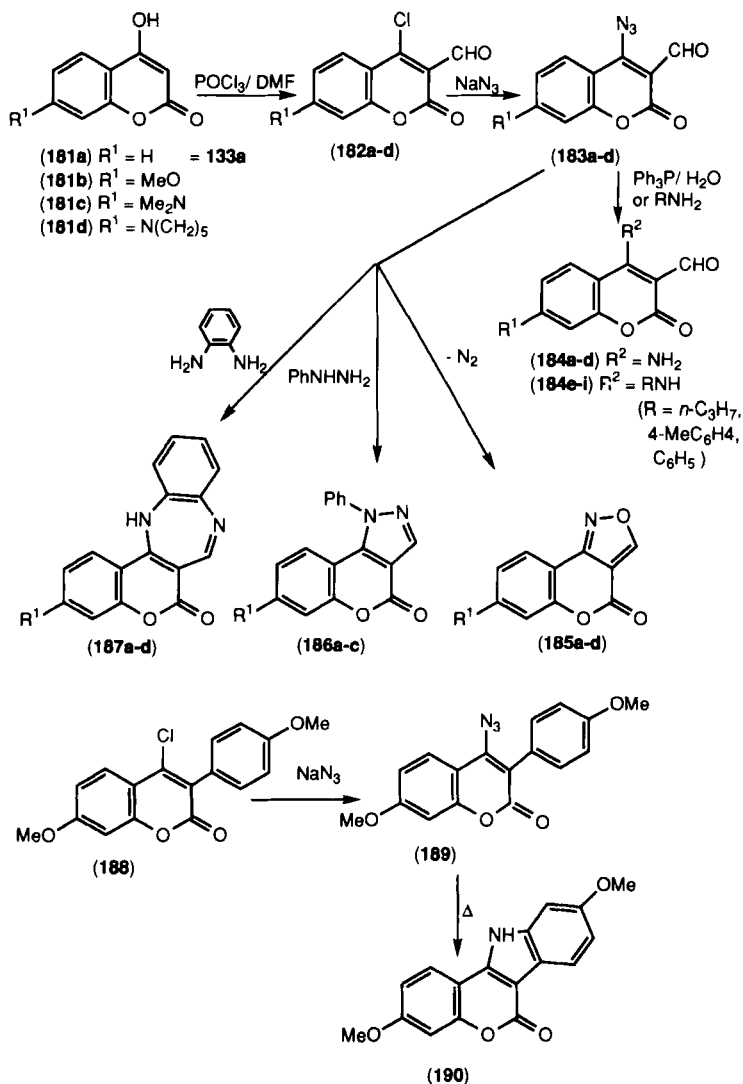
Scheme 33 shows that the methylthio group on 6-aryl- and 6-styryl-3-cyano-4-methylthio-2H-pyran-2-one derivatives **131** reacts readily with



SCHEME 33

various amines to yield the corresponding 4-aminopyrone derivatives **179** in good yields [88SC1919; 90IJC(B)624]. Reaction of **131** with N_2H_4 gives pyrazolopyranone **180**.

Reaction of 4-hydroxycoumarins **181a-d** with $POCl_3$ and DMF (Scheme 34) gives 4-chloro-3-coumarincarbaldehydes **182a-d** (92LA23), and treatment of **182a-d** with NaN_3 gives 4-azido-3-coumarincarbaldehydes **183a-d**.



SCHEME 34

The azides **183a–d** are useful starting materials for the synthesis of a variety of 3,4-disubstituted coumarins, **184a–d** and **184e–i**, as well as heterocyclic [c]-fused coumarins, such as isoxazoles **185a–d**, pyrazoles **186a–c**, and 1,5-diazepines **187a–d**, under mild conditions. In these reactions, **183a–d** are, despite their thermolability, superior to **182a–d**. 4-Chloro-3-aryl-coumarin **188** undergoes thermolytic ring closure, reacting with NaN_3 in refluxing DMF to yield indolo[3,2-*c*]coumarin **190** via 4-azidocoumarin **189** (91M853).

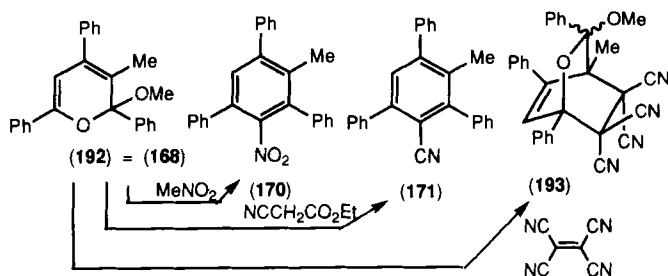
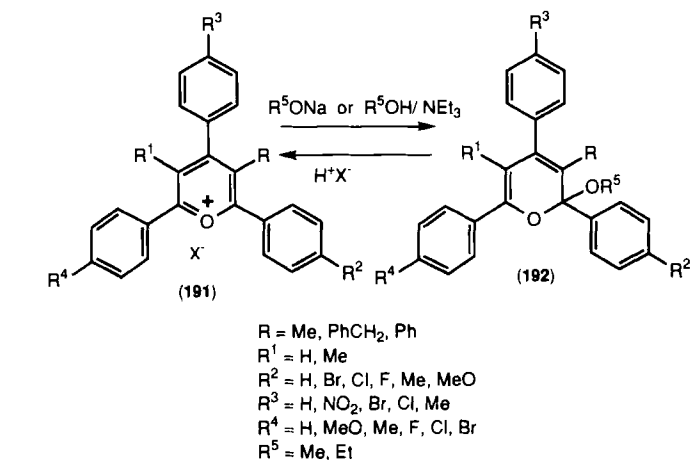
The reactivity of pyrylium ions with azides has been discussed theoretically on the basis of extended Hückel molecular orbital (EHMO) calculations (84T3549). As long as the pyrylium ring is hindered, the most favorable approach of the reactants corresponds to a reaction coordinate yielding azidopyrans. However, when the ring approach is free, the system can assume a geometry that allows the formation of a stable complex.

C. REACTIONS WITH OXYGEN NUCLEOPHILES

1. Reactions of Pyrylium Salts

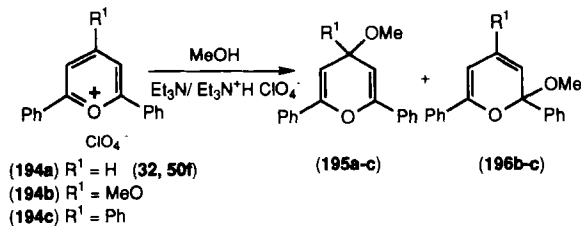
Regioselective addition of NaOR^5 ($\text{R}^5 = \text{Me}, \text{Et}$) to 2,4,6-triarylpyrylium salts **191** (Scheme 35) gives high yields of colorless crystals, i.e., alkoxy-pyrans, which are also prepared by refluxing **191** in R^5OH with NEt_3 as a proton acceptor (81ZC446; 83JPR729). Acid treatment of **192** regenerates the original pyrylium cation **191**. Treatment of **192** with $(\text{NC})_2\text{C}=\text{C}(\text{CN})_2$ gives the cycloadduct **193**, and reaction of **192** with MeNO_2 or $\text{NCCH}_2\text{CO}_2\text{Et}$ gives pentasubstituted benzene derivatives **170** and **171**.

The addition of methoxide ion to 2,6-diphenyl-, 4-methoxy-2,6-diphenyl-, and 2,4,6-triphenylpyrylium cations **194a–c** to give **195** and **196** (Scheme 36) has been studied spectrophotometrically in MeOH in the presence of an $\text{Et}_3\text{N}/\text{Et}_3\text{NH}^+\text{ClO}_4^-$ buffer system (79JOC4496). Rate and equilibrium constants for the addition of the 4-position of **194a** and to the 2- and 4- positions of **194b–c** are determined or estimated at 25°C. The equilibrium constants ($K_4 = >10^7$, $\sim 3 \times 10^6$, and $\sim 7 \times 10^6$) are evaluated for the formation of the 4*H*-adducts **194a–c**, respectively. The rate of *ipso* attack at the 4-position decreases in the order $\text{H} > \text{MeO} > \text{Ph}$ for the 4- R^1 substituents; this is mainly due to ground-state stabilization for $\text{X} = \text{Ph}$ (81JOC960). The lower rate of addition to the methoxy-bearing position of **194b** with respect to that of addition to the hydrogen-bearing position of **194a** is explained in terms of electronic and other structural effects. The α -position is more reactive by a factor of 4.6 in the pyrylium ion **194c**, while the γ -position is more reactive by a factor of 12.5 in **194b** (82JOC960).

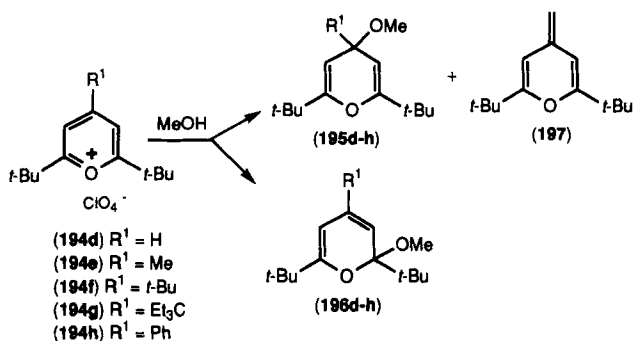


SCHEME 35

The kinetic and equilibrium constants for the reaction of 2,6-di-*t*-butyl-4- R^1 -pyrylium cations **194d–h** with methoxide ion to yield the corresponding 4-*H* and 2-*H* adducts **195d–h** and **196d–h** (Scheme 37) have been determined in MeOH at 25°C (88JOC1729). The reaction involves the



SCHEME 36



SCHEME 37

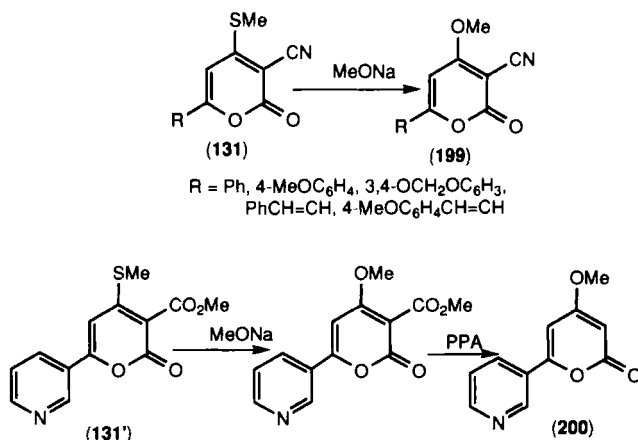
kinetically controlled formation of the 4-*H* adduct **195d-h** only when $R^1 = H$ or Me; in other cases, a mixture of both the 4-*H* and 2-*H* adducts is formed. The 2-*H* adducts **196d-h** are thermodynamically favored products, although a comparable amount of the anhydro base **197** is also formed in the case of the methyl-substituted cation. The rate constants for the formation of the 4-*H* adducts **195d-h** follow a regular trend, showing a low sensitivity to steric effects; the corresponding equilibrium constants are not affected by the steric interactions until a certain value of the steric hindrance of the γ -substituent is reached.

2. Reactions of Pyrone Derivatives

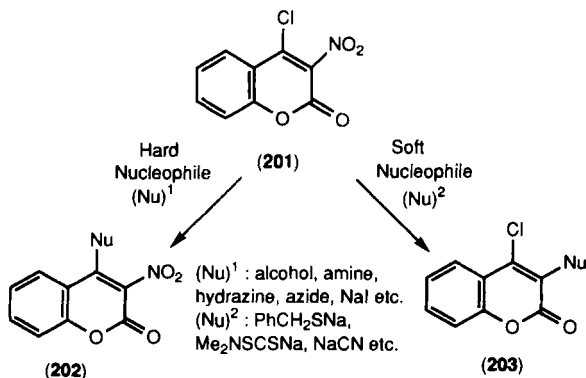
The methylthio group on 6-aryl- and 6-styryl-3-cyano-4-methylthio-2*H*-pyran-2-one derivatives **131** reacts readily with MeONa to yield the corresponding 4-methoxypyrene derivatives **199** in good yields (84CPB3384). (See Scheme 38.) Pyridylpyrone **131'** undergoes substitution with MeONa followed by treatment with polyphosphoric acid to give anibine **200** in 58% yield (84CPB1665).

Reaction of 4-chloro-3-nitrocoumarin **201** with a variety of nucleophiles (Scheme 39) produces a number of novel substituted coumarins **202** and **203** (83LA1901). Hard and borderline nucleophiles exclusively substitute chlorine in the 4-position to give **202**, while soft nucleophiles substitute the nitro group in the 3-position (except for iodide) of **201** to yield **203**. This result of the nucleophilic substitution of **201** is rationalized in terms of Pearson's HSAB (hard and soft acids and bases) model.

4-Oxochromene-3-carbaldehydes **204a-e** cyclize to the corresponding tetrahydrofuro[2,3-*b*][1]benzopyran-4-one **205a-e** in 53, 65, 70, 40, and 65%

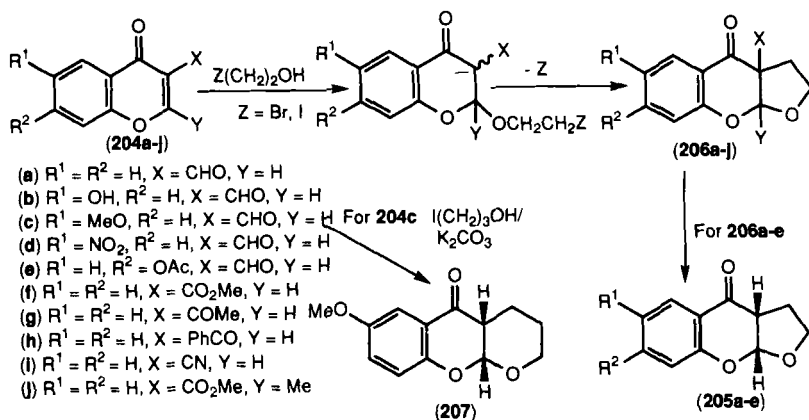


SCHEME 38



SCHEME 39

yields, respectively, on refluxing with $\text{I}(\text{CH}_2)_2\text{OH}$ and K_2CO_3 in Me_2CO for 4 h (84CC1698). The reaction (Scheme 40) probably involves base-induced intramolecular alkylation of an iodoethoxy intermediate to give **206a–e**, followed by deformylation to give **205a–e**. Chromones (4-oxo-4*H*-1-benzopyrans) **204f–j** bearing electron-withdrawing substituents at C₃ react with 2-haloethanols and potassium carbonate in acetone to produce tetrahydrofuro[2,3-*b*][1]benzopyran-4-ones **206f–j** in 24–80% yield, depending on the substituents (91T9431). The similar reaction of **204c** with an excess of 3-iodopropanol produces the *cis* fused tricycle **207** in 26% yield.

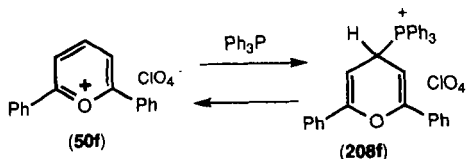


SCHEME 40

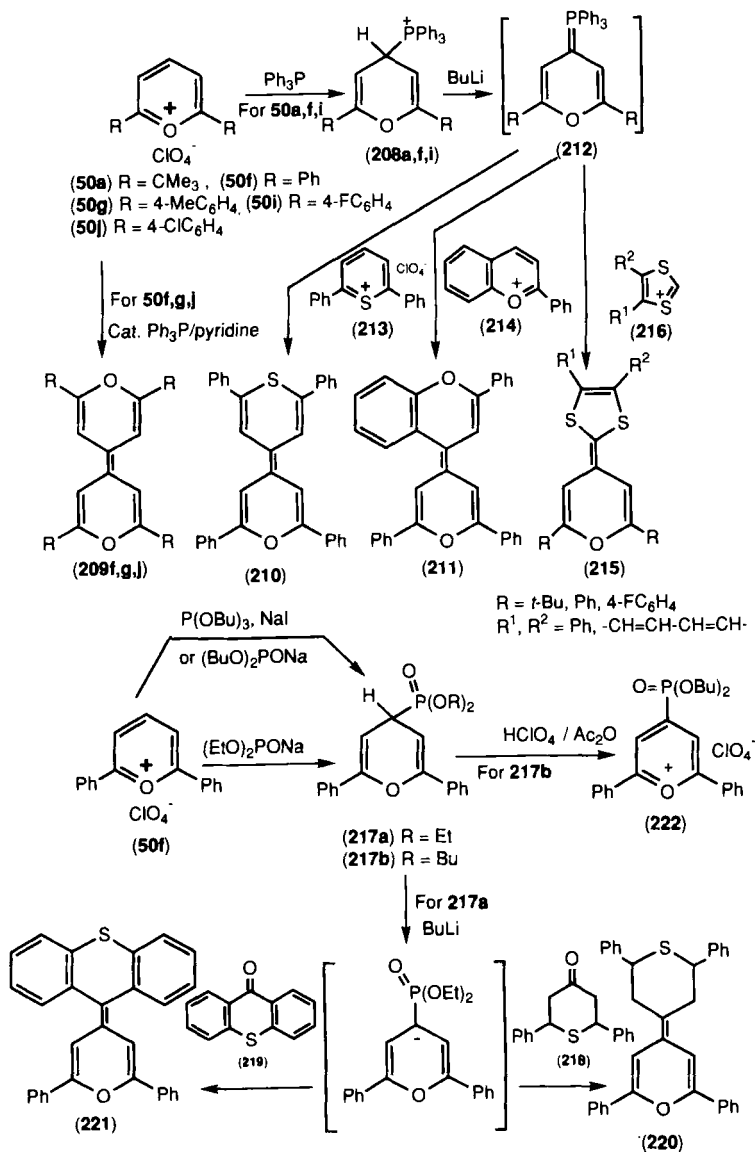
D. REACTIONS WITH PHOSPHORUS, SULFUR, AND OTHER NUCLEOPHILES

An adduct of 2,6-diphenylpyrylium perchlorate **50f** with Ph_3P has salt structure **208f**, not a charge-transfer complex structure (Scheme 41) (89ZOB1506). The crystal structure of **208f** has been determined. Reversible cleavage of the phosphorus-carbon σ -bond in the dissociation of pyranilphosphonium salt **208f** to **50f** and PPh_3 has been studied by electronic spectroscopy, polarography, cyclic voltammetry in MeCN, and NMR in CD_3CN (88DOK359). The dissociation constant is $8.9 \times 10^{-3} M$. Lowering the temperature increases the concentration of **208f**. The degree of dissociation of the adducts of a pyrylium salt and Ph_3P depends on the electron-acceptor properties of the heteroaromatic cation.

As shown in Scheme 42, treatment of 2,6-diarylpyrylium salts **50f,g,j** with a catalytic amount of Ph_3P in pyridine gives bis-2,6-diaryl-4-bipyranylidene **209f,g,j** via phosphonium salts **208f,g,j**, though **209f** has been prepared from **50f** and an equimolar amount of trimethylphosphine in refluxing pyridine (70TL645; 79JOC4456). Unsymmetric $\Delta^{4,4'}$ -bi-4*H*-pyrans **210** and



SCHEME 41



SCHEME 42

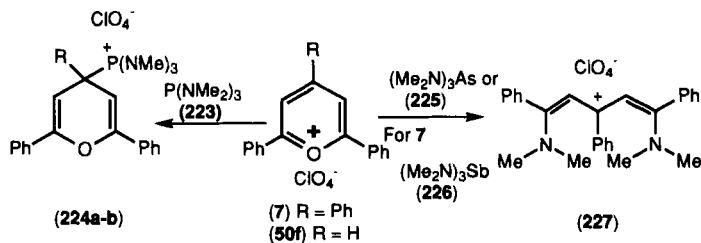
211 are prepared from the Wittig reagents derived from (4*H*-pyranyl)triphenylphosphonium salts (**208f**) by allowing the reagent to react at the 4-position of pyrylium salts **213** and **214** (80JOC2458). By the same methodol-

ogy, **50a,f,i** are transformed via the (pyran-4-yl)phosphonium salts **208a,f,i** into the (pyran-4-ylidene)phosphoranes **212**, which yield the pyranylidene derivatives **215** by reaction with dithiolium salts **216** in 45–56% yield (85JHC1179).

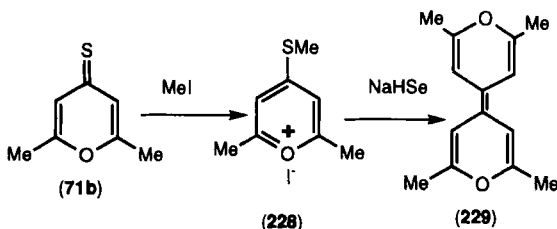
A phosphonate has been synthesized by an ambient-temperature reaction of xanthylium ion with trimethyl phosphite in the presence of NaI (77S862). Although treating 2,6-diphenylpyrylium salt **50f** with trimethyl phosphite in the presence of NaI fails to give the desired phosphonate **217**, even under forcing conditions, diethyl(diphenyl)pyranyl phosphonate **217a** is successfully prepared by adding an equimolar amount of sodium diethyl phosphonate in benzene solution to **50f** in dry THF at -78°C (80JOC2449). This reagent condenses with ketones such as **218** and **219**, leading to the Δ^4 -2,6-diphenyl-4*H*-pyrans **220** and **221** in 61 and 65% yields, respectively. Reaction of **50f** with $\text{P}(\text{O}i\text{Bu})_3$ and NaI proceeds via the Arbuzov rearrangement to give 79% of **217b**, which is also formed in 88% yield by the Michaelis–Becker reaction of **50f** with $\text{NaP}(\text{O})(\text{O}i\text{Bu})_2$ (80ZOB467). Treating **217b** with perchloric acid in Ac_2O gives 14% of **222**.

Reaction of pyrylium salts **50f** and **7** with tris(dimethylamino)phosphine **223** (Scheme 43) affords the phosphonium adducts **224a–b**, whereas treatment of **7** with tris(dimethylamino)arsines **225** and the stibine homolog **226** leads a new series of pentamethinium salts, e.g., **227** (92TL1741).

As Scheme 44 shows, methylation of 2,6-dimethyl-4*H*-pyran-4-thione **71b** with MeI gives the pyrylium ion **228**, which undergoes selenation with



SCHEME 43



SCHEME 44

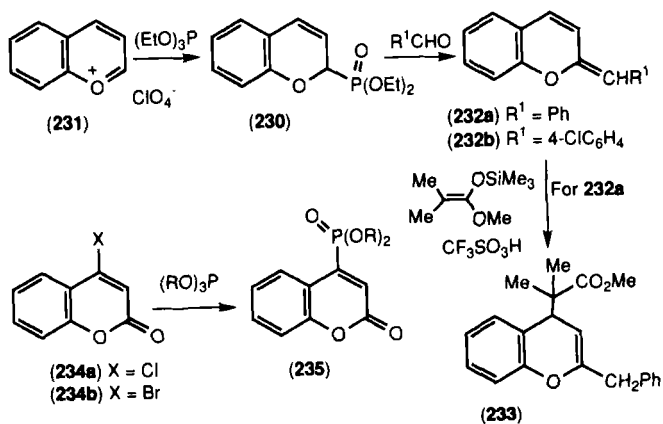
NaHSe in refluxing octane to give bis-2,6-dimethyl-4-bipyranylidene **229** (86ZOR2019).

Benzopyranphosphonic acid derivative **230** (Scheme 45) is prepared by the Arbuzov reaction of **231** (87H2857), while the Wittig reaction of **230** with $R^1\text{CHO}$ ($R^1 = \text{Ph}$, 4- ClC_6H_4) gives the benzylidene-substituted compounds **232a–b**. Treatment of **232a** with $\text{CF}_3\text{SO}_3\text{H}$ and $\text{Me}_2\text{C}=\text{C}(\text{OSiMe}_3)\text{OMe}$ leads to **233**. Treating 4-halocoumarins **234a–b** with 3 *M* excess $(\text{RO})_3\text{P}$ ($R = \text{Me}$, Et) at 135–140°C gives the phosphonate **235** in 17–50% yield (91ZOB2123).

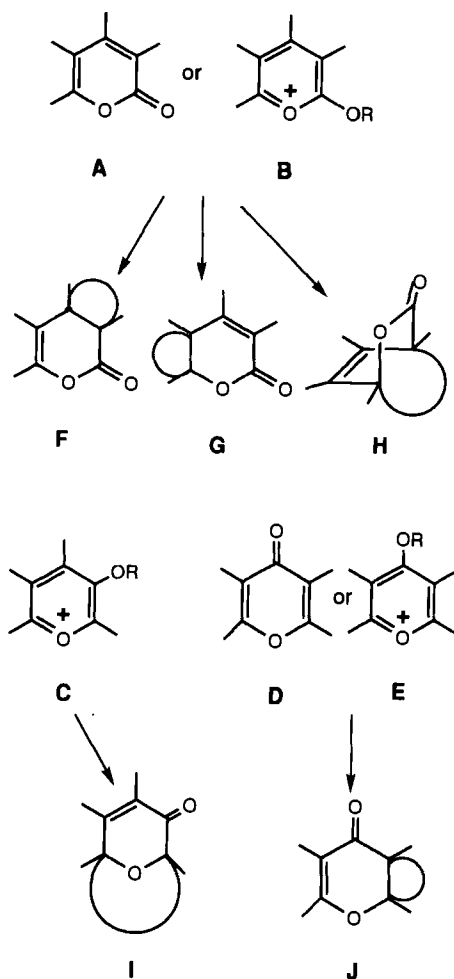
III. Annulation Reactions in Pyrylium Salts and Pyrone Derivatives

Because of their aromatic character, pyrones undergo annulation reactions and the introduction of substituents less readily than do most cyclic α,β -unsaturated carbonyl compounds. Nevertheless, some suitable modifications have been developed that allow these compounds to be used effectively in annulation reactions. Some reviews about synthesis of 2-pyrones with 3,4-fused carbocyclic ring systems are currently available (82S337; 86G109; 92T9111).

Cycloaddition reactions in pyrone derivatives **A** and **D** and activated pyrones **B**, **C**, and **E** (Scheme 46) with pyrylium-ion character are important in synthetic methodology because the initial bicycloadducts **F–J**, which can have up to four contiguous stereocenters as well as variously membered rings (3, 4, 5, 6, 7, etc.), can be formed in one procedure. These bicycload-



SCHEME 45



SCHEME 46

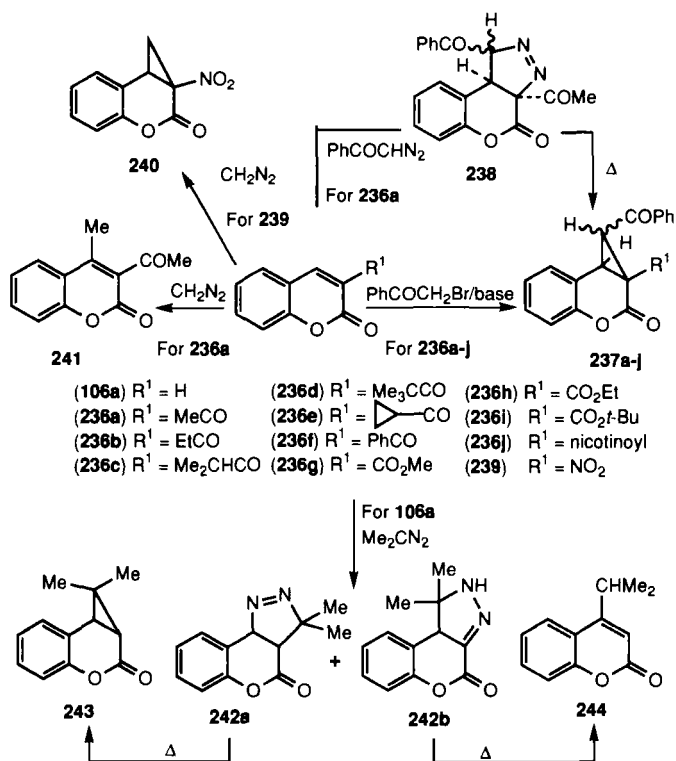
ducts can be a rich source of highly functionalized, stereospecifically substituted synthetic building blocks.

A. [2 + 1]-ANNULATION REACTIONS

Condensation of 3-acetylcoumarin **236a** with phenacyl bromide in the presence of NaOEt gives 3,4-phenacylidene-3-acetylcoumarin **237a** ($R^1 =$

MeCO) [18CB533, 18CB907; 67CI(L)159]. The same compound **237a** has also been prepared by heating (180°C) pyrazoline **238** obtained from 3-acetylcoumarin **236a** and diazoacetophenone (60JA439). Similarly, various 3-acyl-2*H*-1-benzopyran-2-ones (3-acylcoumarins) **236a-j** react with phenacyl bromide in the presence of a base to give a mixture of geometric isomers of cyclopropane derivatives **237a-j** (*cis* and *trans*) in moderate to high yields (93T2275). (See Scheme 47.) The yields of the reaction products are substantially improved by using a catalyst [Aliquat 336 (tricaprylmethylammonium chloride) or TPBP (benzyltriphenylphosphonium chloride)] under phase-transfer conditions.

Cyclopropanation of coumarin derivatives with diazoalkanes (Scheme 47) is one of the general [2 + 1]-annulations, but the product distribution depends on various factors: substituents, the structures of their alkyl groups, reaction conditions, etc. [70JCS(C)897; 76TL1227]. Diazomethane reacts with 3-nitrocoumarin **239** to give the cyclopropane derivative **240**, but also



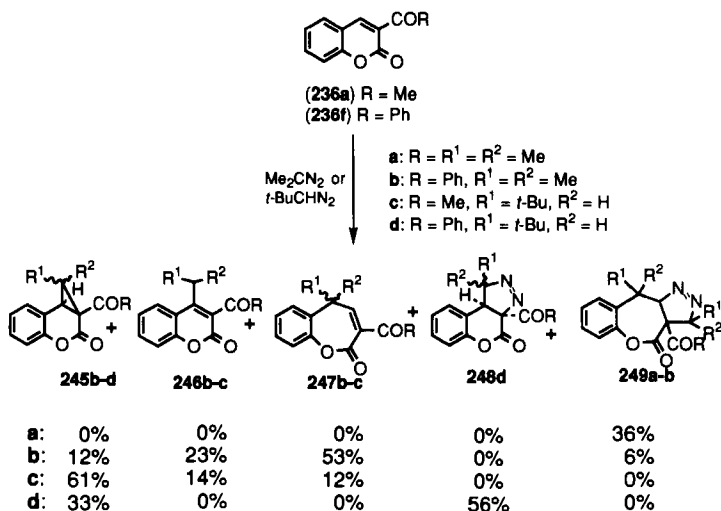
SCHEME 47

rapidly reacts with 3-acetylcoumarin **236a** to afford the 4-methylated derivative **241** (78CC461).

A mixture of pyrazolocoumarin isomers **242a–b** is obtained from coumarin **106a** and Me_2CN_2 (87H2425). Heating **242a** in refluxing xylene gives 95% of **243**, while **242b** is converted into 4-isopropylcoumarin **244** in a 55% yield.

As shown in Scheme 48, reaction of 3-acetylcoumarin **236a** with Me_2CN_2 does not give the cyclopropane derivative, but rather the ring expansion compound followed by inverse cycloaddition of the diazoalkane giving benzoxepinopyrazolone **249a** (36%) [80JCS(P1)2937]. In a similar reaction with 3-benzoylcoumarin **236f**, the inverse cycloaddition is slow enough for the isolation of a small amount of the cyclopropane derivative **245b** (12%) together with the lactone **247b** (53%) and the 4-isopropyl derivative **246b** (23%). Me_3CCHN_2 converts 3-acetyl- and 3-benzoylcoumarin **236a,f** into the cyclopropane compounds **245c** (61%) and **245d** (33%) along with other products such as 4-neopentyl derivatives **246c** (14%), the ring-expansion compound **247c** (12%), and the pyrazoline derivative **248d** (56%), respectively. Decomposition by heating **248d** gives **245d** in 68% yield.

Cyclization of 3-ethoxycarbonylcoumarin **236h** with $(\text{MeO})_2\text{CHCHN}_2$ gives the diastereomeric fused pyrazolines **250a** (*cis* 65%; *trans* 30%, referring to the geometry between the ethoxycarbonyl and the dimethoxymethyl groups) which then undergo photolysis to give a mixture of cyclopropaben-



SCHEME 48

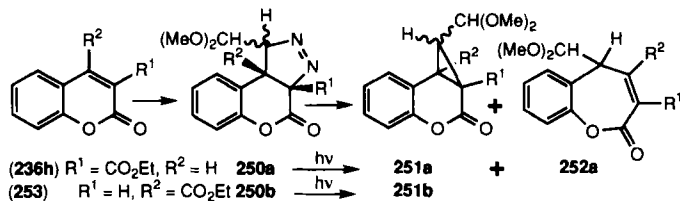
zopyrans **251a** (*cis* 75%; *trans* 17%) and benzoxepine **252a** (8%). Similarly, *trans*-**250a** gives **251a** (*cis* 10%; *trans* 80%) and **252a** (10%). By the same procedure, **253** gives pyrazolines **250b** (*cis* 44%; *trans* 56%), which then photolyze to the cyclopropane compounds **251b** (*cis* 35%; *trans* 57%) (84BSF338). (See Scheme 49.)

Reaction of 3-methoxycarbonylchromone **254a** with $(\text{OMe})_2\text{CHCHN}_2$ gives a mixture of regioisomeric pyrazolines, which either undergo thermolysis to afford **256a** (*cis* 12%; *trans* 25%, referring to the geometry between the methoxycarbonyl and the dimethoxymethyl groups) and **257a** (63%) or $\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$ -catalyzed decomposition to furnish **256a** (*cis* 24%; *trans* 52%) and **257a** (12%). (See Scheme 50.) Reaction of 3-acetyl-6-methylchromone **254b** with 2-diazopropane gives the cyclopropane derivative **256b** (17%) along with 3-acetyl-2-isopropyl-6-methylchromone **257b** (65%). 2-Ethoxycarbonyl-6-methylchromone **254c** reacts with the same diazo compound to give the cyclopropane derivative **256c** (25%) along with the 1-benzoxepine derivative **258** (39%) [81JCS(P1)224]. 3-Nitrochromone (**254d**) undergoes rapid cycloaddition reactions with R_2CN_2 ($\text{R} = \text{Me}$ at -70°C ; $\text{R} = \text{H}$ at 20°C) to give the cyclopropabenzopyranones **256d-1** (37%) and **256d-2** (93%), respectively [80JCS(P1)2049].

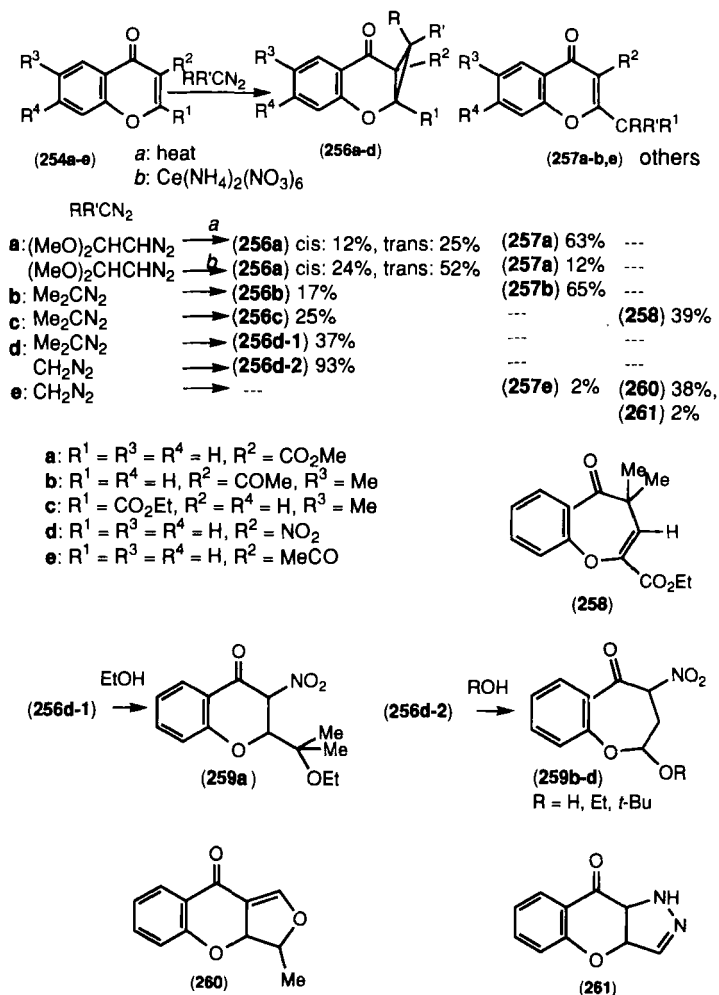
Reaction of **256d-1** with EtOH gives mainly the chromanone **259a**. Compound **256d-2** is cleaved by H_2O and/or alcohols to give the corresponding dihydrobenzoxepinones **259b-d**. 3-Acetylchromone **254e** reacts with CH_2N_2 to give a mixture of 3-acetyl-2-methylchromone **257e** (2%), furochromenone **260** (16%), and pyrazole **261** (2%) [87IJC(B)128].

Reaction of chromones **262a-h** with $\text{Me}_2\text{S}^+(\text{=O})\text{CH}_2^-$ in Me_2SO gives the homochrome derivatives **263a-h** in 10–90% yield, depending on the substituents (R^1 , R^2 , R^3 , R^4) (Scheme 51) [68JCS(C)2302; 76BCJ245; 80MI1; 90H749].

Monocyclopropanation of 4-pyrones **264a-c** with $\text{Me}_2\text{S}^+(\text{=O})\text{CH}_2^-$, using $\text{Me}_2\text{SO}/(\text{Me}_2\text{N})_3\text{PO}$ in place of neat Me_2SO , gives the homo-4-pyrone derivatives **265a-c** (15–53%), which are then rearranged into the 2-furylacetone derivatives **266a-c** (12–40%) together with the hydrated triketones **267a,c** (20–34%) or the dehydrated naphtho[2,1-*b*]furan deriva-



SCHEME 49

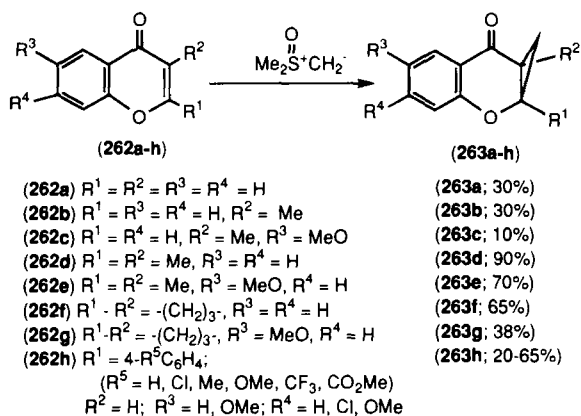


SCHEME 50

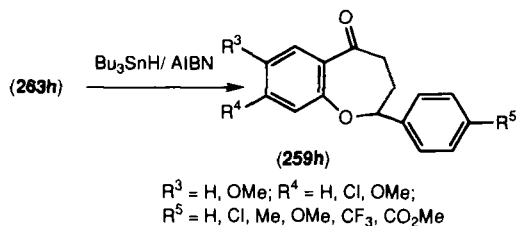
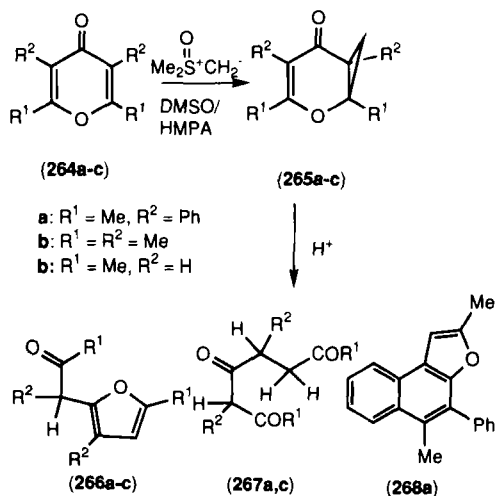
tive **268a** (6%) by means of strong acid (CF₃CO₂H or TsOH) catalysis at room temperature (80BCJ469). Reductive cleavage (Bu₃SnH, AIBN) of the cyclopropane ring affords phenylbenzoxepines **259h** (90H749). (See Scheme 52.)

B. [2 + 2]-ANNULATION REACTIONS

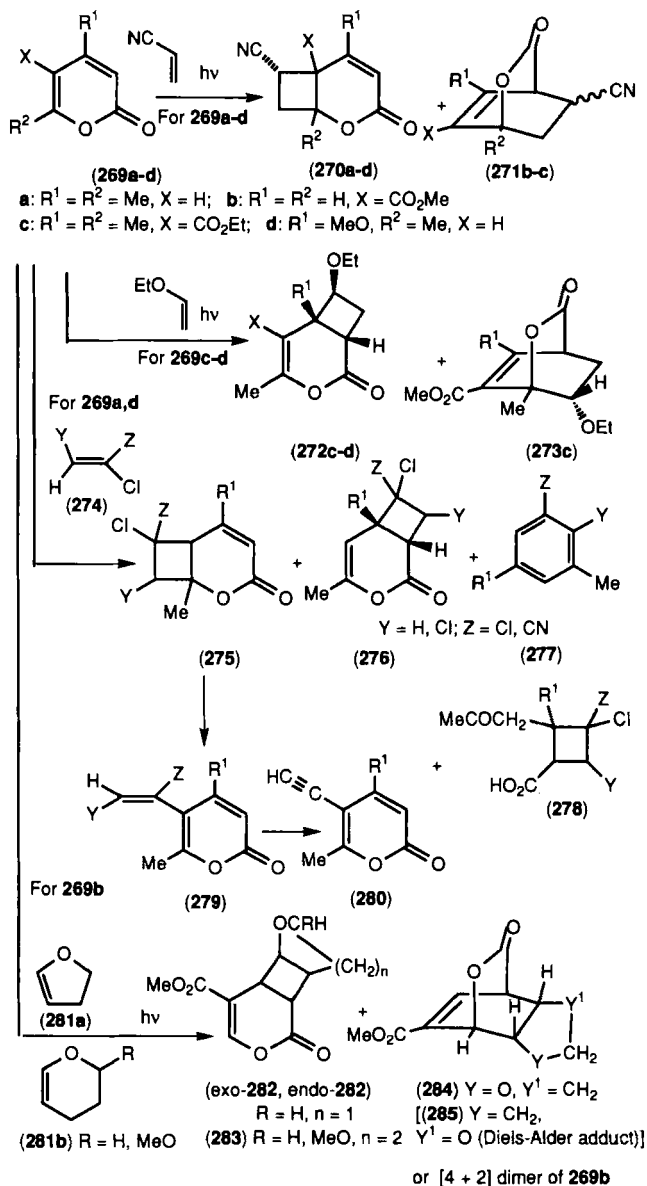
Some investigations of photochemical cross-cycloaddition of pyrone derivatives were reported before 1980 [75JA154; 77JCS(P1)2458].



SCHEME 51



SCHEME 52



SCHEME 53

In Scheme 53, we see that the benzophenone-sensitized photoreaction of 4,6-dimethyl-2-pyrone **269a** with acrylonitrile gives mainly the [2 + 2]-cycloadduct **270a** (61%) across the C_5-C_6 double bond in **269a**, whereas

5-methoxycarbonyl-2-pyrone **269b** affords the [4 + 2]-cycloadduct **271b** (29%) along with a small amount of the [2 + 2]-cycloadduct **270b** (9%) (82NKK1927; 86H3031). Similarly, sensitized photoreactions of 2-pyrones **269c–d** with acrylonitrile give the [2 + 2]-cycloadducts **270c** (61%) and **270d** (46%) across the C₅–C₆ double bonds in the pyrones and the [4 + 2]-cycloadducts **271c** (16%), respectively (90BCJ3456). However, reactions with an electron-donating ethylene, ethyl vinyl ether, give the [2 + 2]-cycloadducts **272c–d** (71–75%) across the C₃–C₄ double bonds in **269c–d** and the [4 + 2]-cycloadduct **273c** (9%) regioselectively. The regioselectivity of **273c** is opposite to that for the thermal [4 + 2]-cycloadduct.

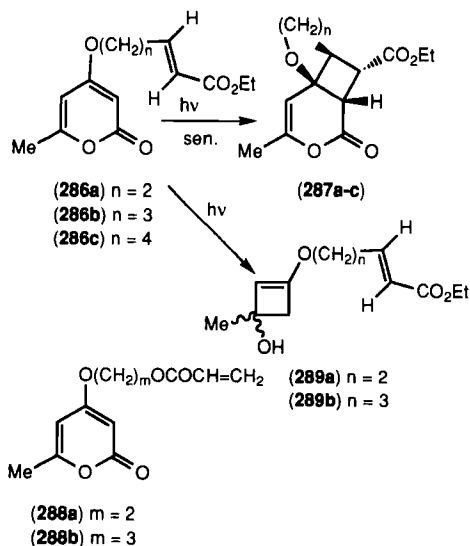
Methylpyrones **269a,d** undergo benzophenone-sensitized photochemical cyclization with vinyl chlorides HCY=CZCl **274** (Y = H, Z = Cl; Y = Z = Cl; Y = H, Z = CN) to give oxabicyclooctenones **275** (R¹ = Me, MeO; Y = H, Cl; Z = Cl, CN) (10–23%), **276** (34%), benzene derivatives **277** (4–17%), and/or cyclobutanecarboxylic acids **278** (5–56%) (87BCJ621). Dehydrochlorination of **275** (R¹ = Me, MeO) with Et₃N in EtOH gives 5-ethenyl-2-pyrones **279**. 5-Ethenyl-2-pyrones **279** having a chlorinated ethenyl group also undergo *anti*-elimination of HCl to give 5-ethynyl-2-pyrones **280**.

The photosensitized (benzophenone) cycloaddition of methyl 2-pyrone-5-carboxylate **269b** with 2,3-dihydrofuran **281a** in benzene gives a mixture of the [2 + 2]-cycloadducts *cis-exo*-**282** (24–38%) and *cis-endo*-**282** (12–16%) and the [4 + 2]-cycloadduct **284**, which is different in orientation from the Diels–Alder adduct **285** (92JHC199). The distribution of products depends on the sensitizer (benzophenone or acetophenone). The photosensitized reactions of **269b** with 3,4-dihydro-2*H*-pyrans **281b** in acetonitrile afford the *cis-endo*-[2 + 2]-cycloadducts **283** (6–12%) along with the [4 + 2]-dimers (15–35%) of **269b**.

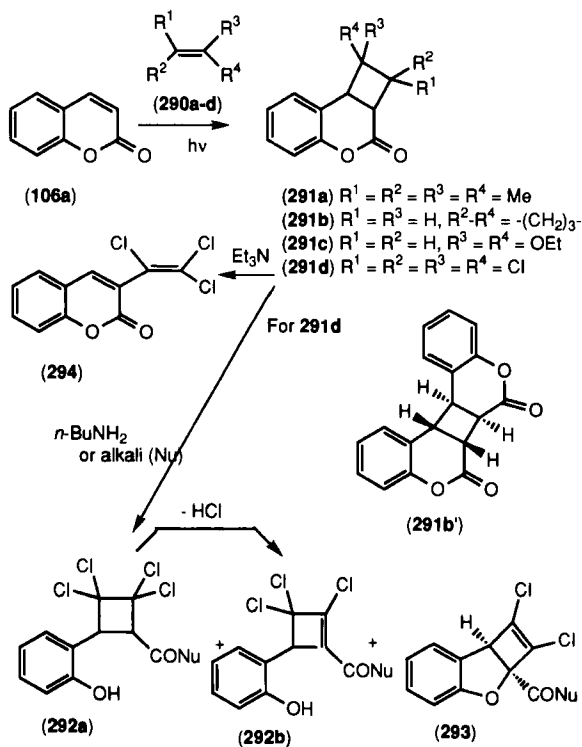
Scheme 54 shows that the photosensitized reactions of pyrones **286a–c** give the intramolecular [2 + 2]-cycloadducts **287a–c** as oxatricyclic lactones, both regio- and stereospecifically; however, **288a–b** give no product. In contrast, direct irradiation of **286a–b** affords cyclobutenecarboxylic acids **289a–b** (91JHC745, 91JOC7150). The intramolecular cycloaddition mechanism has been explained by using the excited state of 2-pyrone calculated by means of the MNDO-CI method.

The photochemical behavior of coumarin and its derivatives has been the subject of numerous investigations. Triplet-sensitized cycloaddition efficiently gives the photodimers and cross-cycloadducts with simple alkenes. A kinetic study on the photocycloaddition of coumarin **106a** has been reported (89JA8653).

As shown in Scheme 55, the photosensitized cycloaddition of coumarin (**106a**) to olefins **290a–c** (tetramethylethylene **290a**, cyclopentene **290b**, and 1,1-diethoxyethylene **290c** in dioxane in the presence of benzophenone

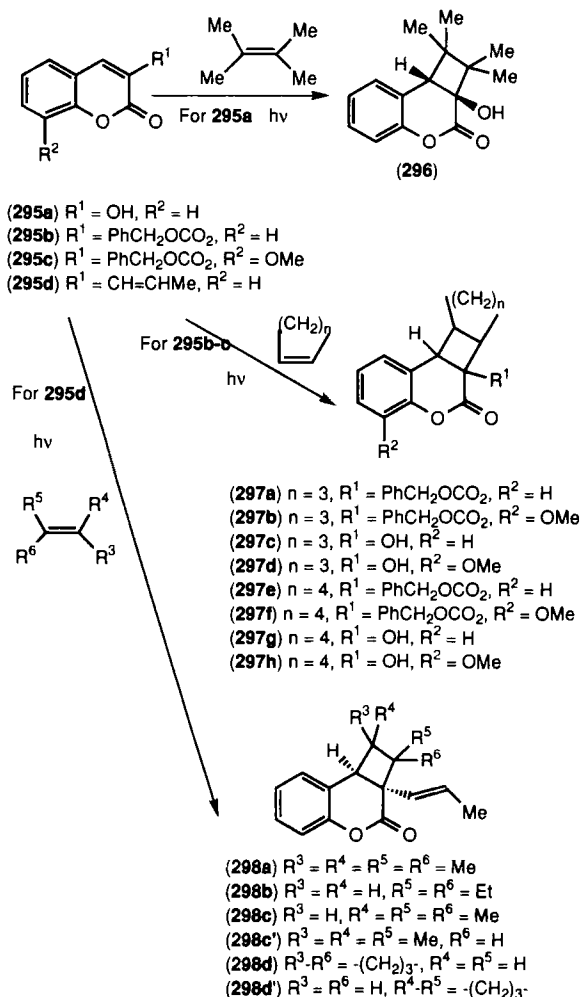


SCHEME 54



SCHEME 55

affords the 1:1 adducts **291a–c** (66TL1419). The sensitized photochemical cycloaddition of coumarin **106a** with cyclopentene gives a sterically unfavorable *cis-cisoid-cis*-adduct **291b** (*cisoid*) (18%) together with a *cis-transoid-cis*-adduct **291b** (*transoid*) (25%) and a head-to-head coumarin dimer **291b'** (21%) with a *cis-transoid-cis* disposition (84CL911; 88BCJ3782). The same reaction of coumarin **106a** with tetrachloroethylene **290d** gives 1,1,2,2-tetrachloro-1 α ,2 α ,2 α ,3 β -tetrahydro-3*H*-cyclobuta[*c*]chromen-3-one **291d** in 31% yield (85JOC3026). Treating **291d** with *n*-butylamine or alkali (NaHCO₃, Na₂CO₃, NaOH, Et₃N) smoothly gives various compounds



SCHEME 56

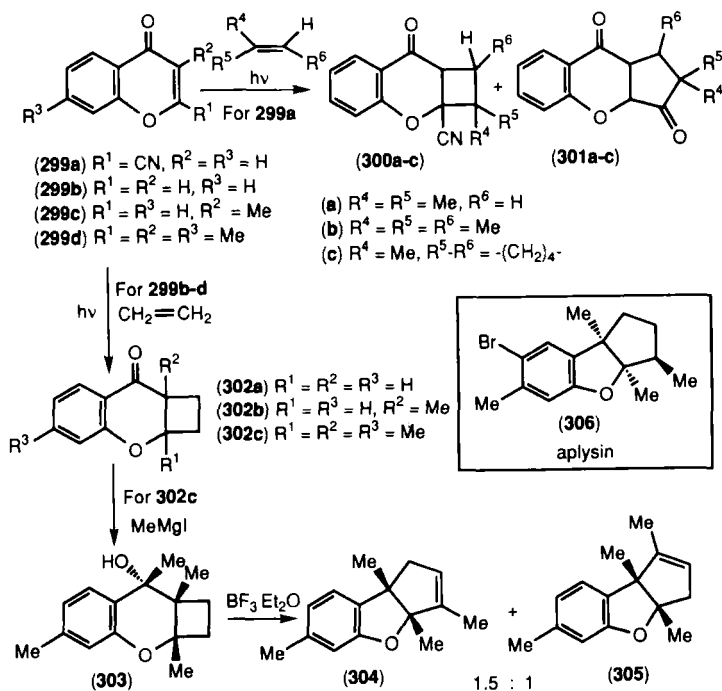
(**292a–b** and **293**) in ratios depending on the reaction conditions. Reaction of **291d** with triethylamine affords exclusively 3-ethenylcoumarin **294**.

Turning to Scheme 56, we see that direct photoaddition of 3-hydroxy-1-benzopyran-2-one **295a** with 2,3-dimethylbut-2-ene in *t*-butyl alcohol gives tetrahydro-2a-hydroxycyclobuta[*c*][1]benzopyran-3-one **296** (63%) arising from [2 + 2]-cycloaddition, whereas photoaddition of 3-(benzyloxycarbonyloxy)-1-benzopyran-2-one **295b** and its 8-methoxy derivative **295c** with cyclopentene gives a 65:35 mixture of the *cis-cisoid-cis* and *cis-transoid-cis* photoadducts **297a** (65%) and a 40:60 mixture of the *cisoid* and *transoid* adducts **297b** (75%) [93JCS(P1)2837]. Removal of the protecting group from **297a–b** by hydrogenolysis of Pd–C as the catalyst affords the *cis-cisoid-cis* isomers **297c** (57%) and **297d** (60%), respectively. The similar [2 + 2]-cycloaddition of the protected 3-hydroxy-1-benzopyran-2-one **295b** and its 8-methoxy derivative **295c** with cyclohexene gives a mixture of the *cis-cisoid-cis* and *cis-transoid-cis* adducts, respectively. Removal of the protecting groups from the photoadducts **297e–f** gives an 85:15 mixture of the *cis-cisoid-cis* and *cis-transoid-cis* adducts **297g** (86%) and a 70:30 mixture of the *cisoid* and *transoid* adducts **297h** (70%), respectively. Efficient photoaddition of 3-(*trans*-1-propenyl)coumarin **295d** with various olefins in benzene occurs to give the corresponding 4- and/or 5-substituted 3-(*trans*-1-propenyl)-3,6-dihydrocyclobut[*c*]-2-coumarin **298a–d** and **298c'–d'** in 37–80% yield without formation of the dimer of **295d** (92TL6465).

Scheme 57 shows that 2-cyanochromone **299a**, upon irradiation in MeOH in the presence of olefins followed by silica gel column chromatography, gives mixtures of the [2 + 2]-cycloadducts **300a–c** (12–55%) and the [3 + 2]-adducts **301a–c** (20–81%) in ratios depending on the olefins (83TL2195). Photocycloaddition of ethylene to chromones **299b–d** affords the adducts **302a** (65%), **302b** (55%), and **302c** (90%). Reaction of **302c** with methylmagnesium iodide gives the cyclobutachromanol **303** (86CC1638; 92JOC1467). Treatment of **303** in benzene with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at room temperature gives a mixture of alkenes **304** and **305** in a 1.5:1 ratio. Alkene **304** possesses the carbocyclic skeleton of the marine natural product aplysin **306**.

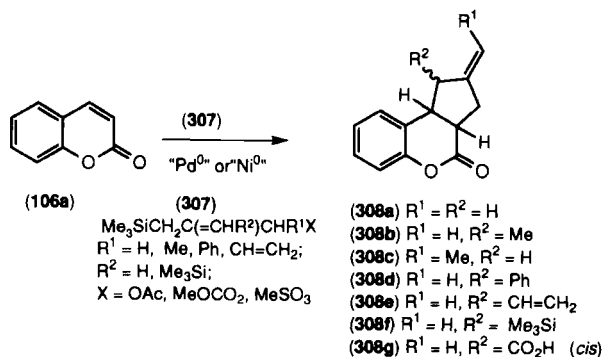
C. [3 + 2]-ANNULATION REACTIONS

The synthesis of five-membered carbocyclic ring fused pyrones has been achieved by two different pathways—one consisting of cycloaddition (a one-step procedure) and the other of a multistep sequence starting with the pyrone ring [01LA27; 64CI(L)1865; 66IJC96]. In this section, some methods for making the five-membered ring via [3 + 2]-cycloaddition are described.



SCHEME 57

2-Trimethylsilylmethylallyl acetate **307a**, readily available from $\text{CH}_2=\text{CMeCH}_2\text{OH}$, provides the equivalent of trimethylenemethane for cycloaddition to electron-deficient olefins in the presence of a $(\text{Ph}_3\text{P})_4\text{Pd}$ complex to give methylenecyclopentanes, normally in 50–85% yields

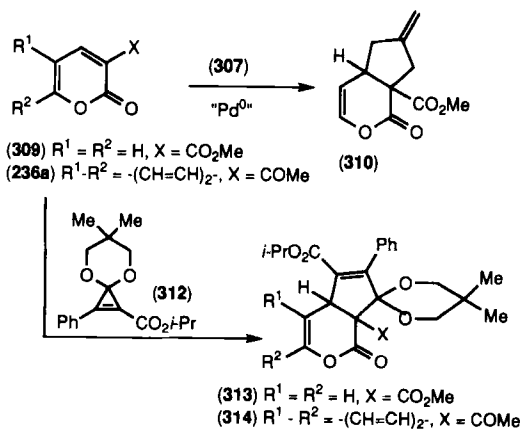


SCHEME 58

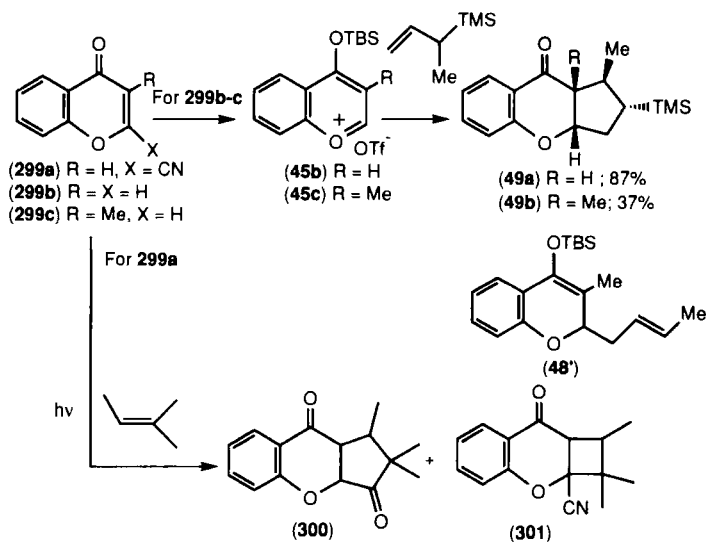
(79JA6429). Thus, reaction of coumarin **106a** with the trimethylenemethane complex (Scheme 58) affords the methylenecyclopentane annulated product **308a** in 52% yield. As catalysts, one can use either preformed $(\text{Ph}_3\text{P})_4\text{Pd}$ or material generated *in situ* by the reduction of $\text{Pd}(\text{OAc})_2$ or trifluoroacetate. In addition to the acetate, the benzoate and methanesulfonate derivatives also participate (80JA6359; 83JA2315). Functionalized trimethylenemethane precursors, $\text{Me}_3\text{SiCH}_2\text{C}(=\text{CHR}^2)\text{CHR}^1\text{X}$ [**307b**] ($\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$, $\text{X} = \text{OAc}$; [**307c**] ($\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$, $\text{X} = \text{OAc}$), **307d** ($\text{R}^1 = -\text{CH}=\text{CH}_2$; $\text{R}^2 = \text{H}$; $\text{X} = \text{OAc}$), **307e** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}_3\text{Si}$, $\text{X} = \text{OAc}$), and **307f** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}_3\text{Si}$, $\text{X} = \text{MeOCO}_2$) undergo cycloaddition with coumarin **106a** in the presence of Pd^0 catalyst to give **308b–g** (81JA5972; 83JA2315; 85JA721; 86JA6051). Treatment of coumarin **106a** with **307g** ($\text{R}^1 = \text{R}^2 = \text{H}$; $\text{X} = \text{MeSO}_3$) in refluxing toluene containing $\text{Ni}[\text{P}(\text{OEt})_3]_4$ overnight also gives 77% of the methylenecyclopentane annulated coumarin **308a** (86CC1201).

[3 + 2]-Cycloaddition occurs between 3-methoxycarbonyl-2-pyrone **309** and a trimethylenemethane $\text{Pd}[(i\text{-PrO})_3\text{P}]_4$ complex to give the cycloadduct **310** in 71% yield (88JA1602). (See Scheme 59.) Reactions of **309** and 3-acetylcoumarin **236a** with cyclopropenone acetal derivative **312** afford regioselectivity the cyclopentenone acetal compound **313** and **314**, respectively (92JA5523).

As shown in Scheme 60, treatment of chromones **299b–c** with *t*-butyldimethylsilyl triflate affords the 1-benzopyrylium triflates **45b–c**. Reaction of **45b–c** with 3-(trimethylsilyl)-1-butene gives the cyclopentane annulation products **49a** (87%) and **49b** (37%) along with a small amount of the allylation product **48'** from **299c** (90CL1725; 91JOC2058).



SCHEME 59



SCHEME 60

Photochemical reaction of 2-cyanochromone **299a** in MeOH in the presence of various olefins followed by silica gel column chromatography gives the [3 + 2]-cycloadducts **300** together with the [2 + 2]-cycloadducts **301** (82TL5439).

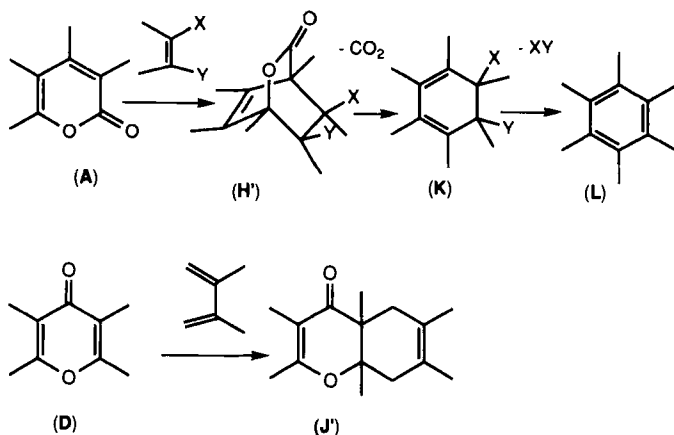
D. [4 + 2]-ANNULATION REACTIONS

2-Pyrones can serve either as dienes (4π -component) or as dienophiles (2π -component) in [4 + 2]-annulation reaction, depending on their reaction partner and their substituents. However, 4-pyrones, coumarins, and chromones react only as the 2π -component (dienophile) with electron-rich dienes. A review of the Diels–Alder cycloaddition of 2-pyrones and related compounds has appeared (92T9111).

1. 4π -Component in [4 + 2]-Cycloadditions

Often CO_2 extrusion occurs at high reaction temperatures in the cycloaddition of 2-pyrones to dienophiles. Further elimination to form regiospecifically substituted aromatic compounds may also take place. (84JOC4033, 84JOC4045). (See Scheme 61.)

Three general solutions have been developed so that these cycloadditions can occur at lower temperatures, thus avoiding the extrusion of CO_2 from

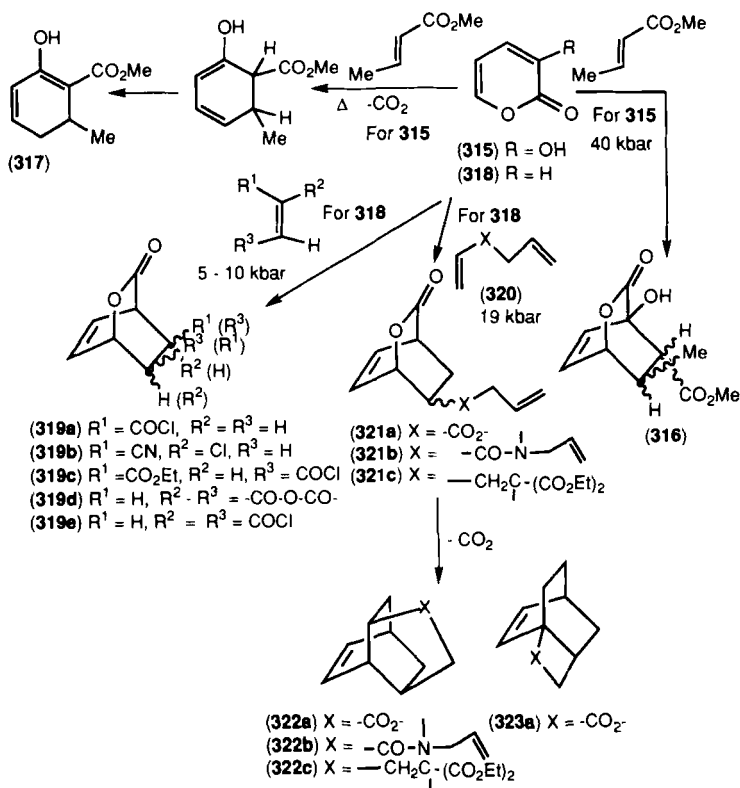


SCHEME 61

the bicycloadduct. The first method involves the use of high pressure so as to facilitate cycloaddition without any modification of diene and dienophile (81H1367; 88MI1; 89MI1; 91MI2, 91T8463). The second method involves substituting the pyrone ring with electron-withdrawing groups while simultaneously making the dienophile more electron-rich or vice versa. The third method is to make either the pyrone diene or the dienophile highly reactive by imposing geometric or electronic constraints on either of these species.

a. *Pressure-Promoted [4 + 2]-Cycloadditions.* High pressure is a perfect technique for accelerating the cycloaddition of 2-pyrone dienes with dienophiles while also suppressing extrusion of CO_2 from the newly formed bicycloadduct. For example, the high-pressure (40 kbar) reaction of 3-hydroxy-2-pyrone **315** and methyl crotonate (Scheme 62) affords quantitatively the adduct as a mixture of *endo* and *exo* isomers **316** (3:2) while the thermal reaction gives the decarboxylation adducts **317** (50%) (75TL2389; 77JOC4170).

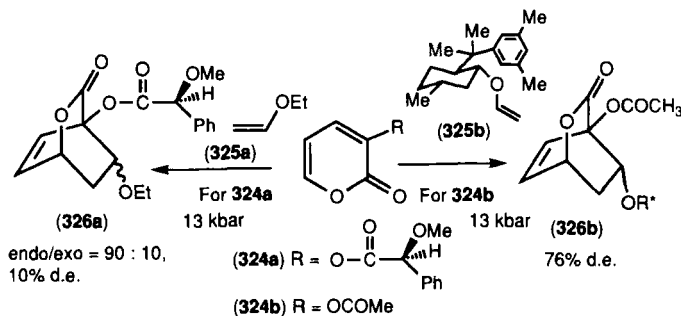
2-Pyrone **318** even reacts with such electron-poor dienophiles as $\text{CH}_2=\text{CHCOCl}$, $\text{CH}_2=\text{CClCN}$, fumaric ethyl ester chloride, maleic anhydride, and fumaroyl chloride at high pressure (5–10 kbar; occasionally, temperatures up to 80°C are employed along with high pressure) to give the adducts **319a–c** as a mixture of regioisomers and **319d–e** (82CB1967). Thus, the 1:1 *endo*- and *exo*-adducts **319d** are obtained in 92% yield. Cycloaddition of 2-pyrone **318** with various substituted acrylates **320** and even an isolated olefin produces the bicycloadducts **321a** (95%), **321b** (95%), and **321c** (45%) under very high pressure (19 kbar) (91TL2549). These



SCHEME 62

initial cycloadducts are obtained with high regiocontrol but usually as a mixture of *endo* and *exo* isomers. By adjusting the pyrolysis temperature, loss of CO_2 and a concomitant intramolecular Diels-Alder reaction take place, leading to the polycyclic adducts **322a** (22%), **322b** (93%), **322c** (95%), and **323a** (65%).

Carboxylate esters **324a-b** (Scheme 63) can cycloadd with electron-rich vinyl ethers at 13 kbar for 7 days (91TL3147). These reactions do not proceed under thermal conditions or by the use of Lewis acids. Furthermore, the asymmetric inverse-electron-demand Diels-Alder reactions of esters **324a** with vinyl ether **325a** proceed under high pressure (13 kbar) at ambient temperature to give the synthetically useful bicyclic adducts **326a** in 94% yield as an *endo/exo* mixture (90:10). The adduct **326b** can be synthesized with diastereofacial selectivity, up to 76% d.e., by the reaction of the acetate **324b** with chiral 8-(3,5-dimethylphenyl)menthyl vinyl ether **325b**.



SCHEME 63

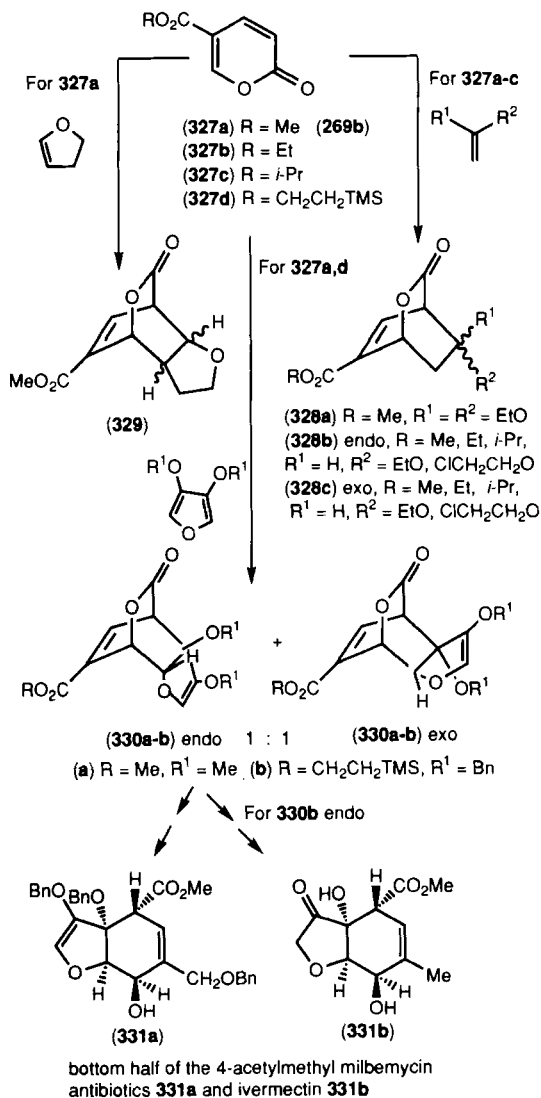
b. *Electronic Matching by Substituent.* The second general device that facilitates cycloaddition and isolation of the bicycloadducts is the matching of the electronic properties of the pyrone diene and dienophile partner.

Reaction of 5-methoxycarbonyl-2-pyrone **327a** (Scheme 64) with 1,1-diethoxyethylene in refluxing benzene affords the bicyclic adduct **328a** in 79–94% yield (69CB2835). Diels–Adler reactions of 5-alkoxycarbonyl-2-pyrones **327a–c** with alkyl vinyl ether $\text{H}_2\text{C}=\text{CHOR}^2$ ($R^2 = \text{Et}, \text{ClCH}_2\text{CH}_2$) give a mixture of *endo*-**328b** (71–83%) and *exo*-**328c** (6–15%) isomers, respectively (82NKK1927; 89NKK1765). The similar reaction of 5-methoxycarbonyl-2-pyrone **327a** with 2,3-dihydrofuran at 60°C in benzene gives the 25% *endo*- and 38% *exo*-adducts **329**.

3,4-Dimethoxy- and 3,4-dibenzyloxyfurans undergo cycloaddition with **327a,d** in MeOH to give with chemo- and regioselectivity a stereochemical mixture of the 1:1 *endo*- and *exo*-adducts **330a–b** in 52 and 88% yields, respectively (86JA6810; 87TL5977; 90BSF830). The latter **330b** (*endo*) is converted into the fully functionalized intermediates **331a–b** for the bottom half of the 4-acyloxymethyl milbemycin antibiotics and ivermectin via several steps.

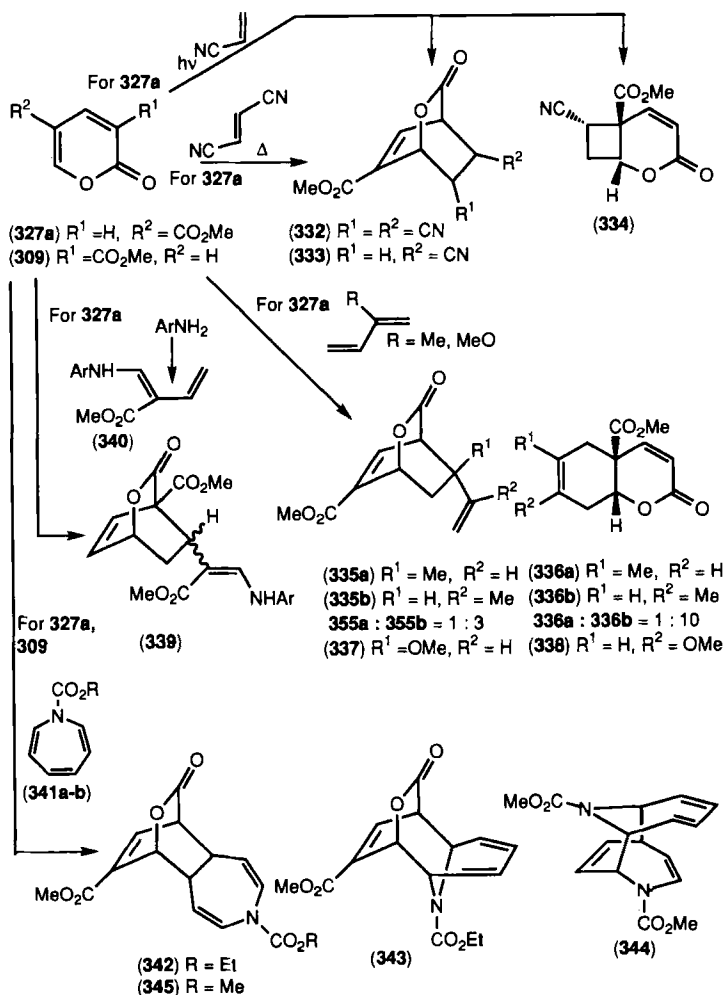
Reaction of methyl coumalate **327a** (Scheme 65) with an electron-poor dienophile such as fumaronitrile at high temperature (120°C, no solvent) gives the [4 + 2]-adduct **332** in 28% yield (89NKK1765). However, the reaction of **327a** with acrylonitrile takes place only under irradiation in the presence of a sensitizer (benzophenone) to give two types of [4 + 2]-cycloadducts **333** (*endo* 17%; *exo* 12%) along with [2 + 2]-cycloadduct **334** (9%).

Reaction of 2-pyrone **327a** with isoprene gives a 1:3 mixture of regioisomers of 3-oxo-2-oxabicyclo[2.2.2]oct-5-ene derivatives **335a–b** (55%) along with a 1:10 mixture of regioisomers (30%) of tetrahydrocoumarin deriva-



SCHEME 64

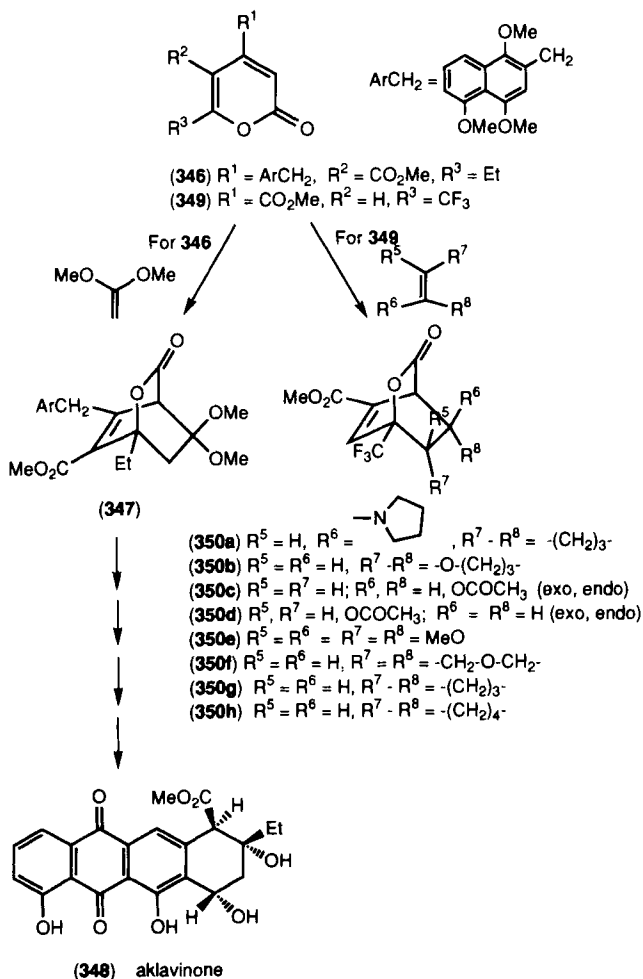
tives **336a-b** (32%) (83BCJ647; 88BCJ316). However, only **337** (10%) and **338** (66%) are obtained in the reaction of **327a** with CH₂=C(OMe)CH=CH₂. Reaction between 2 equivalents of 2-pyrone **327a** and 1 equivalent of substituted aromatic amine ($pK_a^* = 1.02-2.8$) gives 2:1 adducts **339** via cycloaddition with conjugated enamines **340** (85HCA1569).



SCHEME 65

Cycloaddition of 2-pyrene **327a** with 1-ethoxycarbonyl-1*H*-azepine **341a** ($R = \text{Et}$) at 80°C gives [4 + 2]- and [4 + 6]-adducts **342** (25%) and **343** (20%), whereas the reaction of **341b** ($R = \text{Me}$) with 3-methoxycarbonyl-2-pyrene **309** at 80°C affords only the [4 + 2]-adduct **345** in 5% yield along with the [6 + 4]-dimer **344** (11%) (84BCJ3483).

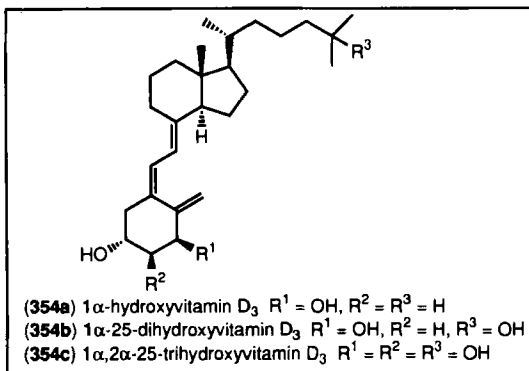
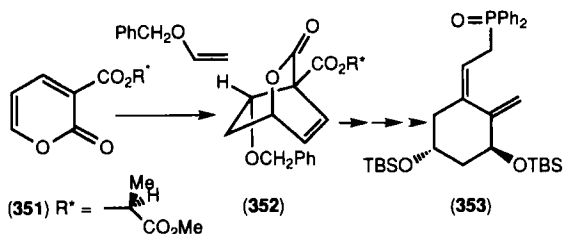
Thermal cycloaddition of **346** (Scheme 66) with 1,1-dimethoxyethylene gives the bicyclic lactone **347** (87JOC1889). The reaction is applicable to the synthesis of aklavinone **348**.



SCHEME 66

6-Trifluoromethyl-2*H*-pyran-2-one derivative **349** has been prepared by starting from the 1:1 adduct $\text{F}_3\text{CCCl}_2\text{CH}_2\text{CCl}(\text{CO}_2\text{Me})\text{CH}_2\text{CO}_2\text{Me}$ of the Cu_2Cl_2 -catalyzed addition of F_3CCl_3 to dimethyl itaconate (85T4057, 85TL3947). The electrophilic 2-pyrone **349** undergoes a [4 + 2]-cycloaddition reaction with various kinds of olefins to give the corresponding adducts **350a-h**.

The Diels-Alder reaction of enantiomerically pure 2-pyrone (*S*)-lactate **351** (Scheme 67) with benzyl vinyl ether at -30°C in the presence of a



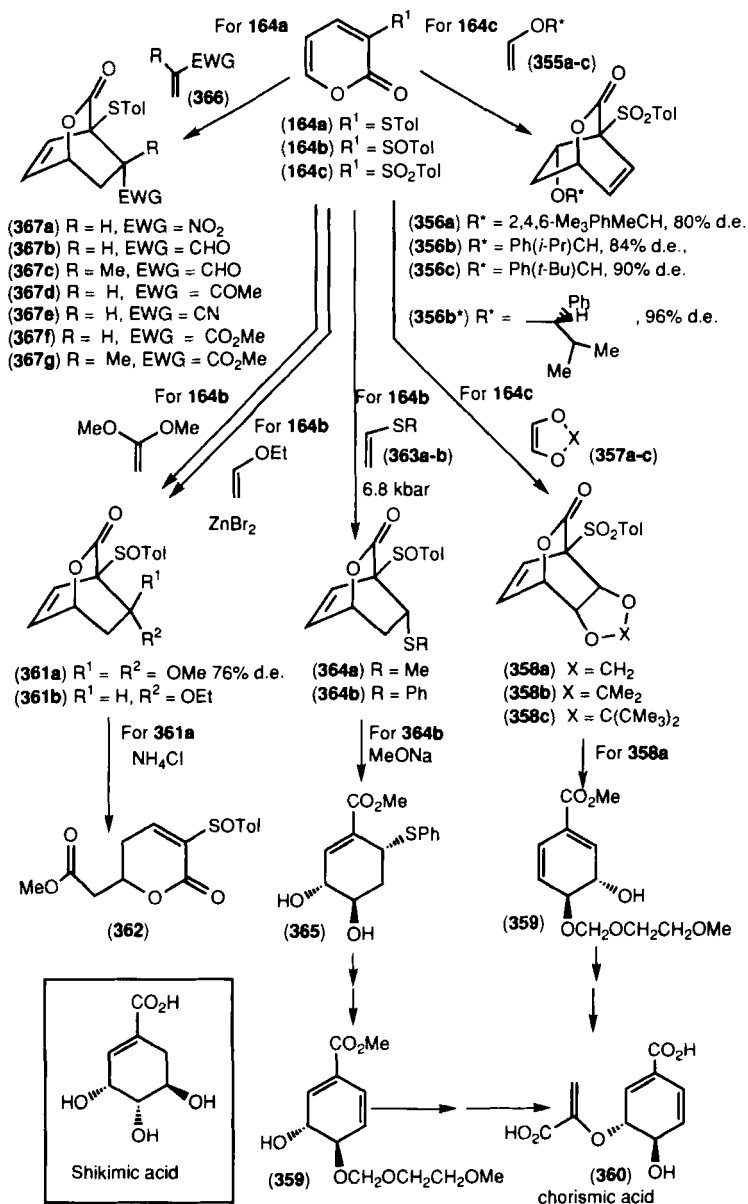
SCHEME 67

chiral Lewis acid and the NMR shift reagent (–)-Pr(hfc)₃ regiospecifically produces quantitatively the *endo* diastereomer (95% d.e.) of bicyclic lactone **352** via a double stereodifferentiation process (92JOC7012). The lactone **352** is transformed smoothly into phosphine oxide **353**, an important A-ring precursor to various physiologically active 1 α -hydroxyvitamin D₃ steroids **354a**.

As shown in Scheme 68, the Diels–Alder cycloadditions of electron-poor 3-sulfonyl-2-pyrone **164c** with chiral alkyl vinyl ethers **355a–c** under mild conditions (25–68°C) afford the bicyclic lactone adducts **356a–c** in excellent yield and with diastereoselectivities of up to 90% d.e. (86TL667; 88JA2650, 88JA3588; 90JOC3967).

Reaction of sulfone pyrone **164c** with enantiomerically pure vinyl ether (*S*)-**355b*** in the presence of a Lewis acid such as [4-Me-2,6-(*t*-Bu)₂C₆H₂O]₂-MeAl at –45°C in 1:1 toluene/methylene chloride gives the cycloadduct **356b*** in 93% yield as a 98:2 ratio of the *endo* diastereomers. This reaction is applied to the synthesis of 1 α ,25-dihydroxyvitamin D₃ (**354b**) (90JOC3967).

Cycloaddition of 3-sulfonyl-2-pyrone **164c** with electron-rich dioxoles **357a–c** [X = CH₂, CMe₂, C(CMe₃)₂] under thermal conditions (80°C) gives bicyclic lactones **358a** (*endo* 78%; *exo* 15%) and **358b** (*endo* 77%; *exo* 23%), while the pressure-promoted reaction (25°C, 11–12.5 kbar) affords 86% of



SCHEME 68

the *endo* and 14% of the *exo* products **358a-c** (90T4573). The bicyclic adducts **358a** are shown to be useful building units, as exemplified by a very short and high-yield preparation of a chorismic acid precursor **359**.

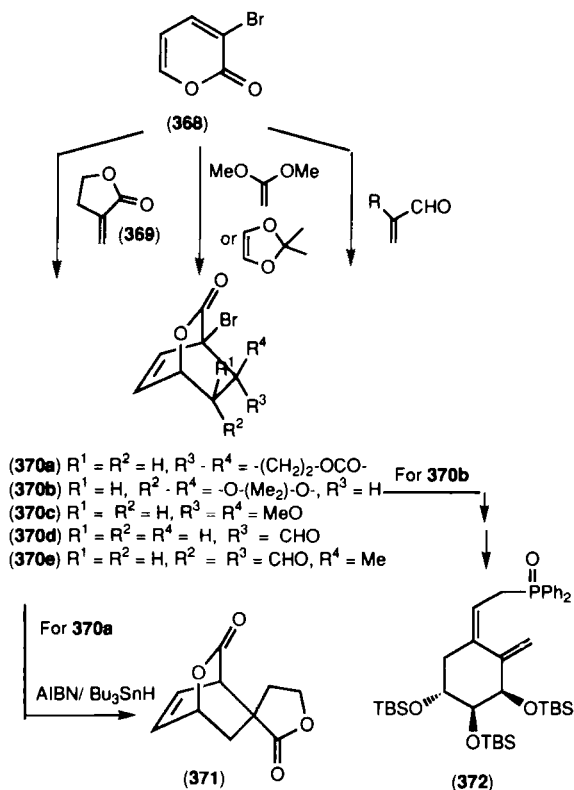
Chorismic acid **360** is known to be a key intermediate in the shikimate biosynthetic pathway that bacteria and lower plants use to convert carbohydrates into aromatic compounds.

Reaction of 3-sulfinyl-2-pyrone **164b** with 1,1-dimethoxyethylene in toluene or hexane at 25°C affords the adduct **361a** (>95%) with high diastereoselectivity (76% d.e.) (85CC1786). Acid treatment of **361a** with NH_4Cl in CH_2Cl_2 leads mainly to the ring-opened and double-bond-isomerized product **362**. Pyrone sulfoxide **164b** is less reactive than pyrone sulfone **164c** as the enophile in inverse-electron-demand Diels–Alder reactions. Cycloaddition between the pyrone sulfoxide **164b** and ethyl vinyl ether requires the use of ZnBr_2 to expedite product **361b** formation (87JOC4836).

Although zinc bromide-assisted cycloaddition of pyrone sulfoxide **164b** fails with thiovinyl ethers **363a–b** ($\text{R} = \text{Me}, \text{Ph}$), the cycloaddition occurs at 6.8 kbar at room temperature to give the *endo* adducts **364a–b**. Methanolysis of **364b** with NaOMe is followed *in situ* by spontaneous [2,3]-sigmatropic rearrangement to give phenylthiocyclohexene *trans*-diol **365** in 66% overall yield from pyrone sulfoxide **164b**. Several chemical transformations lead to monoprotected cyclohexadiene *trans*-diol **359**, which has been converted into chorismic acid **360** (78CC869; 82JA6787; 85JOC888; 87JOC1765).

3-Sulphenyl-2-pyrone **164a** undergoes cycloaddition with a variety of electrophilic olefins **366** to form the isolable bicycloadducts **367a–g** under sufficiently mild thermal conditions ($\leq 90^\circ\text{C}$) in moderate to very good yields (42–82%) without loss of CO_2 (92JOC4083). These bicyclic adducts **367a–g** are formed regiospecifically and often with excellent stereoselectivity (*endo:exo* ratio >98:2 for **367a–d**, 2:1 for **367e**, and 3:1 for **367f–g**).

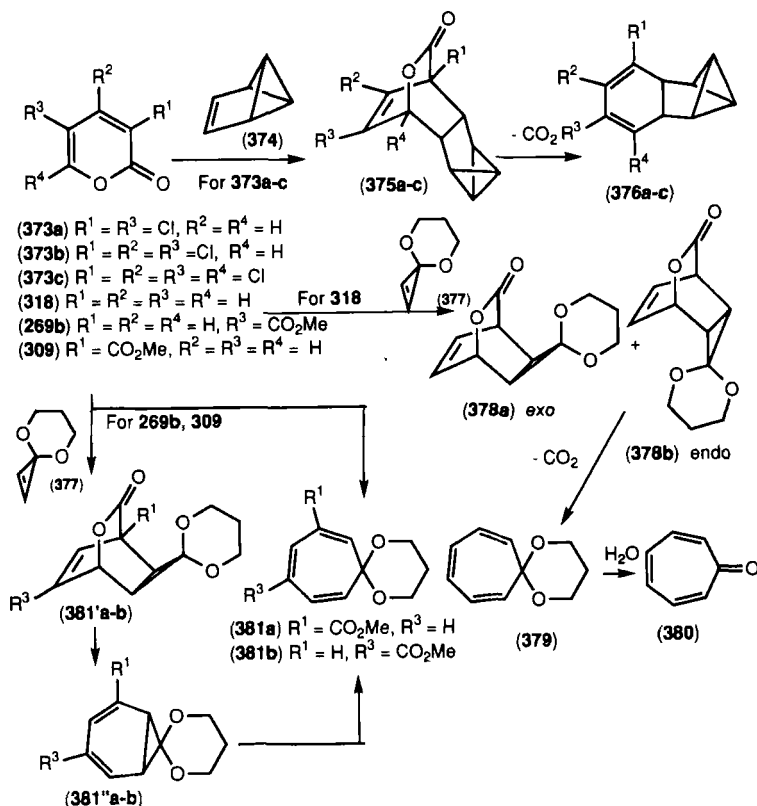
3-Bromo-2-pyrone **368** (Scheme 69) can serve either as a nucleophilic or an electrophilic substrate in the Diels–Alder reaction depending on the reaction partners. Thus **368** undergoes cycloaddition with 2-methylene-4-butenolide **369** to give bromospirofuranoneoxabicyclooctenone **370a** (*endo:exo* = >95:5) in 70% yield. Reductive debromination of **370a** with Bu_3SnH and AIBN gives the halogen-free cycloadduct **371** in 89% yield (91TL5295). Therefore, 3-bromo-2-pyrone **368** is a practical and effective synthetic equivalent of 2-pyrone in thermal Diels–Alder reactions. Reaction of **368** with electron-rich and electron-poor olefins gives cycloadducts **370b** (*endo:exo* = 4:1), **370c**, **370d** (*endo:exo* = 98:2), and **370e** (*endo:exo* = 98:2) in 33–63% yield, respectively. However, the bromopyrone **368** is less reactive as a nucleophilic diene than the 2-pyrone sulfide **164a**. The Diels–Alder *endo*-adduct **370b** is transformed into trihydroxylated A-ring allylic phosphine oxide **372** as an immediate precursor to $1\alpha,2\alpha,25$ -trihydroxyvitamin D_3 **354c** (91JOC4339).



SCHEME 69

c. *Activated Dienophiles and/or Dienes.* When the pyrone or dienophile is activated by imposing geometric or electronic constraints on either of these species, the Diels–Alder cycloaddition smoothly proceeds at lower temperatures without CO₂ extrusion. The reactions of chloropyrones **373a–c** with benzvalene **374** give adducts **375a–c**, which eliminate CO₂ on heating to form cyclohexadienes **376a–c** (85CB979). (See Scheme 70.)

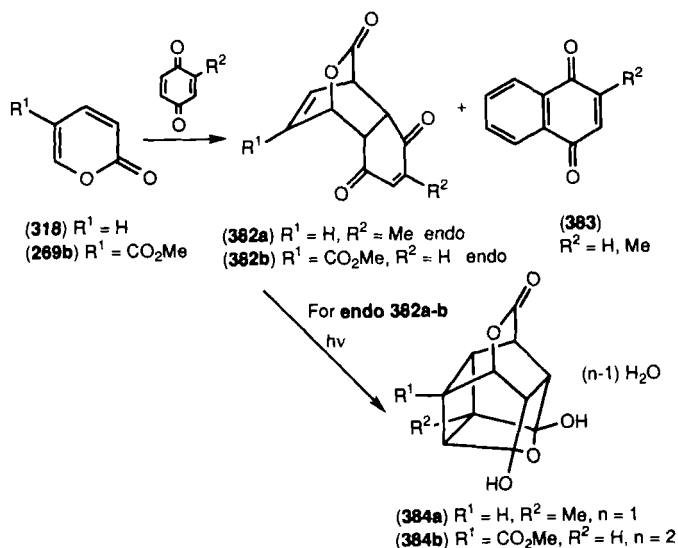
The pressure-promoted [4 + 2]-cycloaddition of 2-pyrone **318** with cyclopropenone ketal **377** (25°C, 6.2 kbar) affords a mixture of reaction products: *exo*-adduct **378a**, cycloheptatrienone ketal **379**, and cycloheptatrienone **380** (resulting from SiO₂ hydrolysis of **379**), each representing the product derived from the Diels–Alder reaction of 2-pyrone **318** with cyclopropenone ketal **377** (86JA6695). The *endo*-adduct **378b** loses carbon dioxide upon depressurization, while the *exo*-adduct **378a** is thermally stable. 3-



SCHEME 70

(Methoxycarbonyl)- and 5-(methoxycarbonyl)-2-pyrone **309** and **269b** provide the cycloheptatrienone ketals **381a-b** directly (25°C, 6.2 kbar). The intermediate [4 + 2]-cycloadducts **381'a-b** or the norcaradienes **381''a-b** cannot be detected or isolated. The results observed are consistent with the potential for the strained olefin of the cyclopropenone ketal to exhibit accelerated participation in both inverse-electron-demand (diene LUMO-controlled) and normal (diene HOMO-controlled) Diels-Alder reactions (86T2777).

Reaction of 2-pyrone **318** (Scheme 71) with *p*-benzoquinone in refluxing benzene gives the *endo*-adduct **382a** (39%) and the *exo*-adduct **382a'** (1%) along with 1,4-naphthoquinone **383** (2%) (82NKK1927). The reaction occurs in other solvents (CH_3CN , EtOH, *t*-BuOH, and toluene) to give the Diels-Alder adducts. Cycloaddition of 5-methoxycarbonyl-2-pyrone **269b** with *p*-benzoquinone gives Diels-Alder adduct **382b** (31%) only in nonpolar

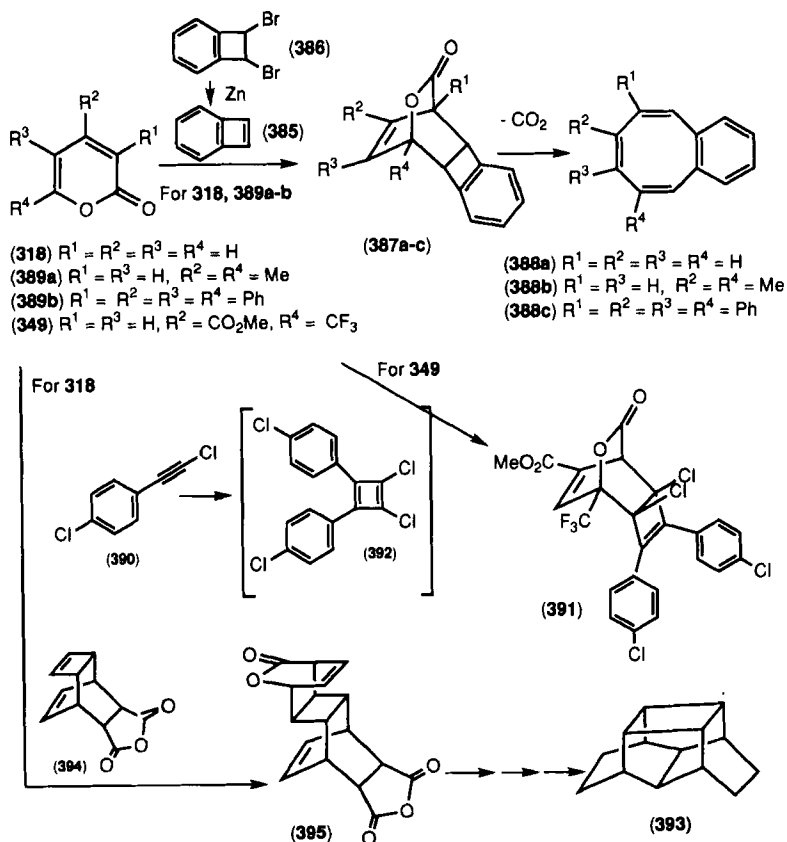


SCHEME 71

solvents such as benzene. The Diels–Alder *endo*-adducts **382a–b** (*endo*) may be irradiated to give the new cage lactones **384a–b** in 75–89% yield (92JHC801).

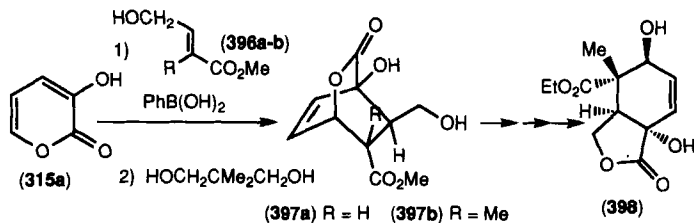
As shown in Scheme 72, benzocyclobutene **385**, generated by debromination of 1,2-dibromo-1,2-dihydrobenzocyclobutene **386** with zinc dust, undergoes cycloaddition with 2-pyrone **318** to give cycloadduct **387a** (44%), which undergoes elimination of CO_2 and valence isomerization in refluxing DMF to give a quantitative yield of benzocyclooctene **388a** [85JCS(P1)-1407]. Similar reactions of **385** with alkyl or aryl derivatives **389a–b** of 2-pyrone give benzocyclooctenes **388b–c** directly at $<100^\circ C$. Reaction of 6-trifluoromethyl-4-methoxycarbonyl-2-pyrone **349** with 4- $ClC_6H_4C\equiv CCl$ **390** gives tricyclic **391** in 70% yield. The acetylenic dienophile **390** undergoes a head-to-head [2 + 2]-cycloaddition to form a reactive substituted cyclobutadiene **392**. Under the reaction conditions, cyclobutadiene **392** then acts as a dienophile through its less hindered double bond (85T4057). Hexacyclo-[6.5.1.0^{2,7}.0^{3,11}.0^{4,9}.0^{10,14}]tetradecane **393** has been prepared by way of **395** from the cyclooctatetraene maleic anhydride adduct **394** and 2-pyrone **318** (86CB3442).

Although reaction between 3-hydroxy-2-pyrone **315a** and 4-hydroxy-2-butenate **396a** ($R = H$) does not occur in refluxing benzene, the cycloaddition in C_6H_6 containing $PhB(OH)_2$ followed by treatment with $HOCH_2C-$



SCHEME 72

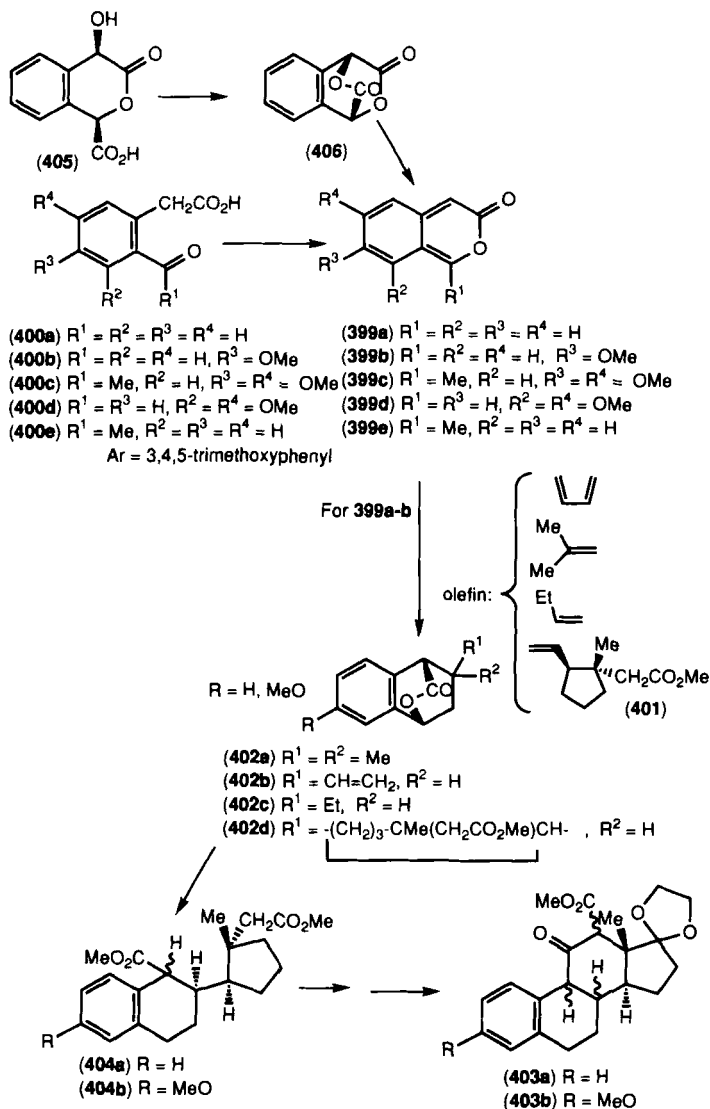
Me₂CH₂OH gives oxabicyclooctene carboxylate **397a** (Scheme 73) (91S1171). The regioselectivity of **397a** is opposite to that of the cycloadduct of **315a** and methyl crotonate under high pressure (75TL2389; 77JOC4170). Under the same reaction conditions, the Diels–Alder reaction of **315a**



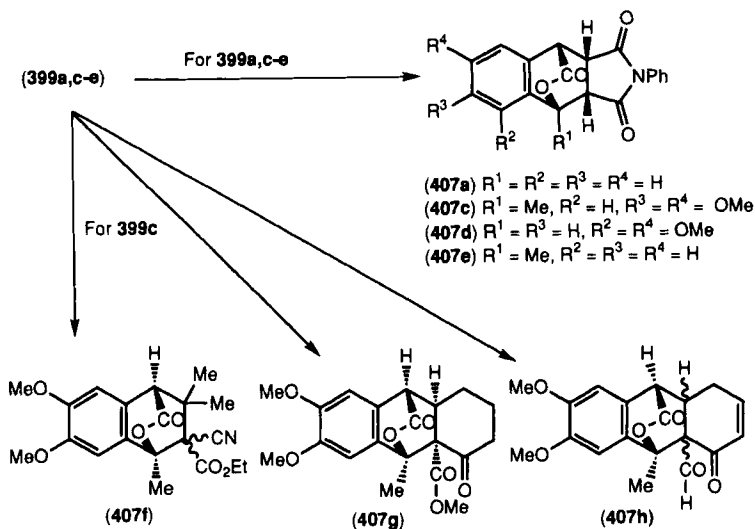
SCHEME 73

with dienophile **396b** ($R = \text{Me}$) gives **397b** ($R = \text{Me}$) with regio- and stereoselectivity, followed by several chemical transformations to afford a fully functionalized CD ring system (**398**) of Taxol (92CC1118).

2-Benzopyran-3-one **399** is also a very reactive diene in the intermolecular Diels–Alder reaction [70JCS(C)536; 76JCS(P1)1647]. (See Schemes 74 and 75.) 2-Benzopyran-3-one **399a–b** derived from **400a–b** undergoes



SCHEME 74

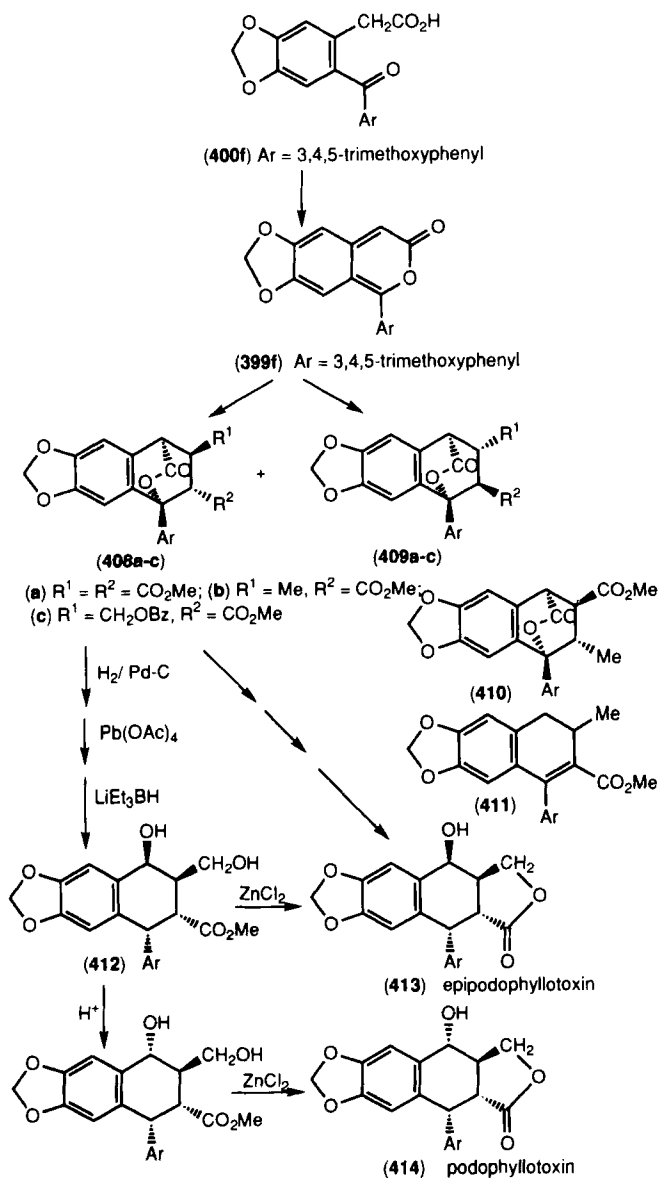


SCHEME 75

strongly regioselective Diels–Alder reactions with 1,3-butadiene, isobutene, 1-butene, and a functionalized olefin **401** to give adducts **402a–d**; the adducts derived from **401** and either **399a** or **399b** are readily transformed into the aromatic steroids **403a–b** by a four-step sequence including the Dieckmann cyclization of **404a–b** (Scheme 74) [85CC1027; 91JCS(P1)1683].

Reaction of *cis*-**405** with Ac_2O – $NaOAc$ in boiling benzene gives **406** in 67% yield (Scheme 74) (83CC1095). Thermolysis of **406** in bromobenzene (156°C) containing *N*-phenylmaleimide gives the *endo* adduct **407a** in 89% yield via the cycloaddition of **399a** with the maleimide (Scheme 75). An alternative procedure for preparation of 2-benzopyran-3-one **399c–e** has been developed [91JCS(P1)639]. Treating *o*-acylphenylacetic acid **400c–e** with DCC/2-hydroxypyridine affords 2-benzopyran-3-ones **399c–e**. Then reaction of **399c–e** with *N*-phenylmaleimide gives the adducts **407c–e** in high yield. The benzopyranones **399c–e** are trapped with various dienophiles to give the Diels–Alder adducts. Thus, reaction of **400c** with 2-isobutoxy-*N*-isobutoxycarbonyl-1,2-dihydroquinoline and $Me_2C=C(CN)CO_2Et$ gives 83% tricyclic benzopyranones **407f** as a 1:1 *cis/trans* mixture. A similar cycloaddition affords the [4 + 2]-adducts **407g–h**.

Reaction of **399f** with dimethyl fumarate in boiling benzene gives the adducts **408a** and **409a**, in a ratio of ~3:1 [87CC1797; 93JCS(P1)2541]. (See Scheme 76.) This ratio rises to 5:1 when the reaction is conducted in MeCN at 50°C; **408a** is then isolated in 76% yield by crystallization of the adduct mixture from EtOH. Furthermore, treatment of **400f** with boiling



SCHEME 76

acetic anhydride leads to quantitative conversion into an isolable pyrone **399f** [93JCS(P1)2533]. Reaction of the pyrone **399f** with methyl crotonate at 90°C without solvent gives the *endo*-CO₂Me adduct **409b** (38%), the *exo*-

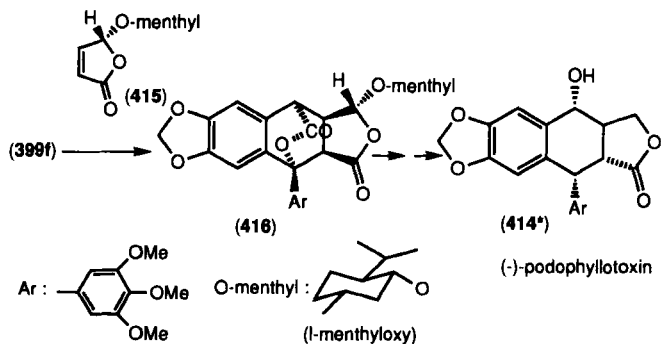
CO₂Me adduct **408b** (24%), the regioisomer **410** (12%), and a minor amount of a product **411** (4%) derived by decarboxylation. Benzopyran-3-one **399f** undergoes Diels–Alder reaction in CH₃CN to methyl 4-benzoyloxycrotonate to give the adduct **408c** regioselectively and stereoselectively. The adduct **408a** is transformed in three steps into methyl apipodophyllate **412**, which gives epipodophyllotoxin **413** (81%) by direct lactonization (ZnCl₂/tetrahydrofuran/4Å molecular sieves) (87CC1797). By the same procedure, including epimerization by acid, the adduct **408c** is transformed into podophyllotoxin **414** [93JCS(P1)2533].

As shown in Scheme 77, addition of **399f** to the chiral dienophile **415** at 50°C in CH₃CN gives **416** with high regio- and diastereoselectivity in 79% yield (93CC1200). By using this reaction, (–)-podophyllotoxin **414*** of 98% optical purity is synthesized in eight steps and 15% overall yield.

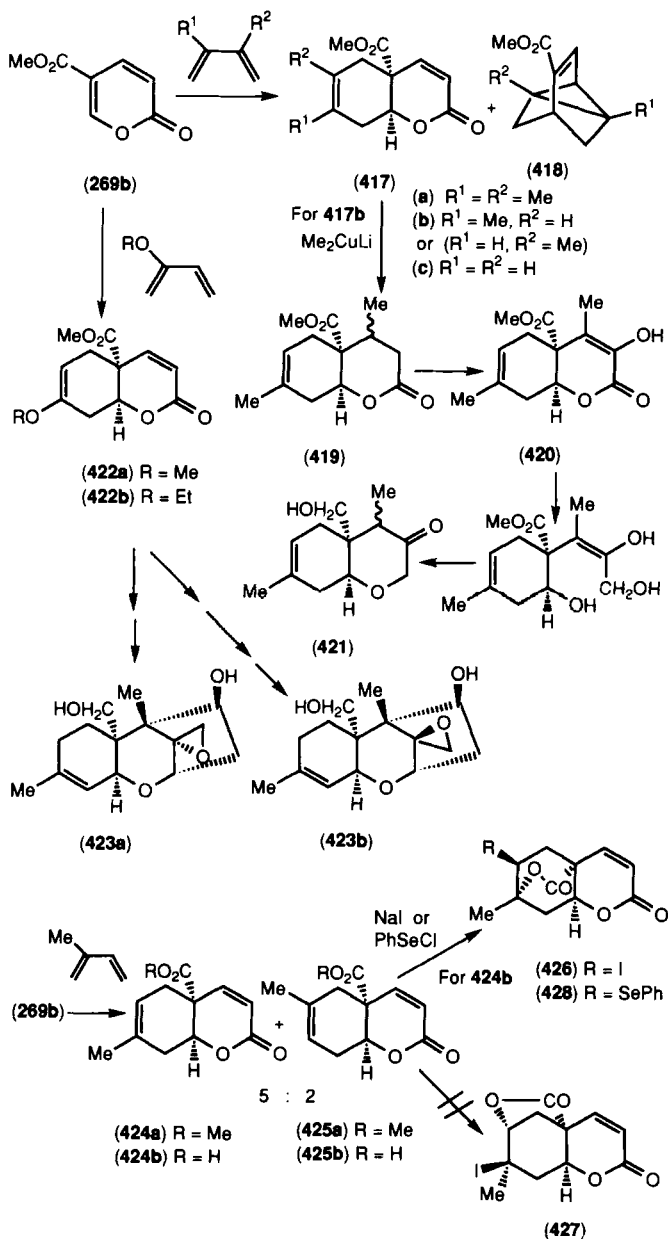
2. 2π-Component in [4 + 2]-Annulation Reactions

Usually, when 2-pyrones participate in [4 + 2]-cycloaddition, they serve as 4π-components. However, there are a few examples in which the 2-pyrone ring behaves as a 2π-dienophile. (See Scheme 78.) Thus, reaction of methyl coumalate **269b** with conjugate olefins (2,3-dimethylbutadiene, isoprene, and butadiene) in benzene at 100°C affords two adducts, **417a–c** and **418a–c**, in ratios of 10 : 1, 4 : 3, and 3 : 4, respectively (72CC388; 74T2227; 79BCJ1506; 80CPB1981).

Transformation of **417b** into lactone **419**, followed by Me₂CuLi addition, hydroxylation, and oxidation with *N*-chlorosuccinimide gives the hydroxy lactone **420** (80JOC4820). Enol ether formation, reduction of the lactone and ester functions, and hydrolysis of the enol ether give hydroxy ketone



SCHEME 77



SCHEME 78

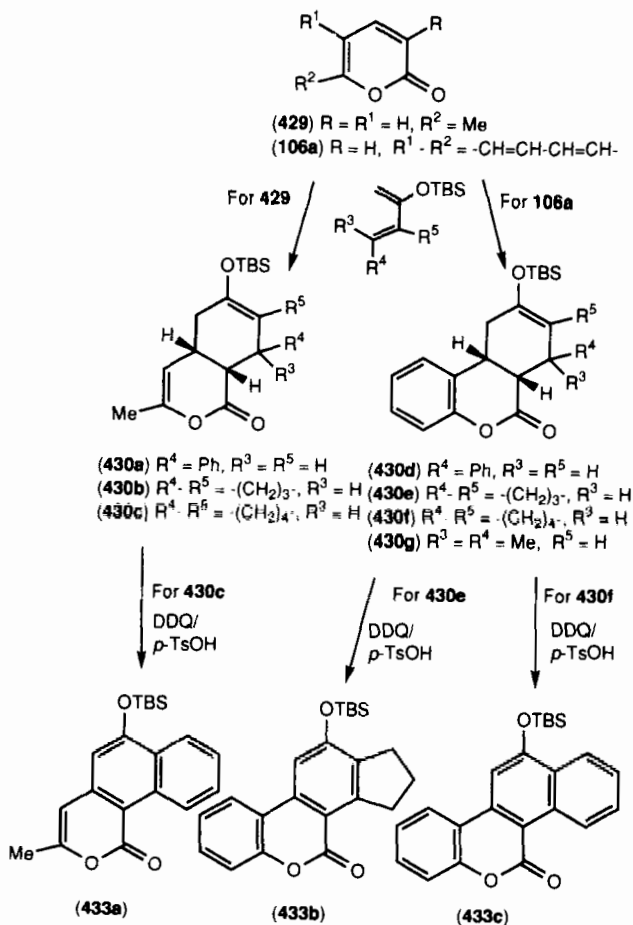
421, an AB synthon for verrucarol **423**. Reaction of **269b** with 2-methoxy-1,3-butadiene gives the adduct **422a**, which is transformed into 12,13-epoxytrichothec-9-ene **423a** in several steps. Diels–Alder reaction of methylcoumalate **269b** with 2-ethoxybutadiene (C_6H_6 , $100^\circ C$) gives a single regioisomer **422b** in 79% yield (81JOC3376). This adduct is transformed via photochemical cycloaddition of acetylene and a cyclobutenyl carbinol to cyclopentenol rearrangement to give the C ring of verrucarol **423b**.

Reinvestigation of the Diels–Alder reaction of methyl coumalate **269b** indicates that the reaction with isoprene gives a mixture of 5:2 regioisomers **424a** and **425a** (15%), followed by hydrolysis to give acids **424b** and **425b** (84CC1514). The cycloaddition employing coumaloyl chloride as dienophile ($110^\circ C$, toluene 45 h) followed by esterification (MeOH, Et_3N) gives **424a** and **425b**. The overall yield is improved to 40% in a ratio of 4:1. Iodolactonization of acid **424b** gives the dioxatricyclododecenedione **426**, not the iodo lactone **427** as previously reported (83BCJ647). Selenolactonization of **424b** with PhSeCl occurs analogously to give **428**.

A new method for using 6-methyl-2*H*-pyran-2-one **429** and 2*H*-1-benzopyran-2-one **106a** as 2π -component in $[4 + 2]$ -annulation has been developed in the reaction of pyrylium triflates with silyloxydienes (90H813). (See Scheme 79.) Thus, reactions of 6-methyl-2*H*-pyran-2-one **429** and 2*H*-1-benzopyran-2-one **106a** with $R^3R^4C=CR^5C(=CH_2)OSiMe_2CMe_3$ [$R^3, R^4 = H, Me, Ph, R^5 = H$; $R = H, R^4R^5 = (CH_2)_n, n = 3, 4$] in the presence of $Me_3CSiMe_2O_3SCF_3$ give the $[4 + 2]$ -cycloadducts **430a–g** (30–68%) regio- and stereoselectively (91JOC5052). The ring junction in the cycloadducts is *cis*. Dehydrogenation of **430c,e,f** with DDQ affords the aromatic compounds **433a–c**.

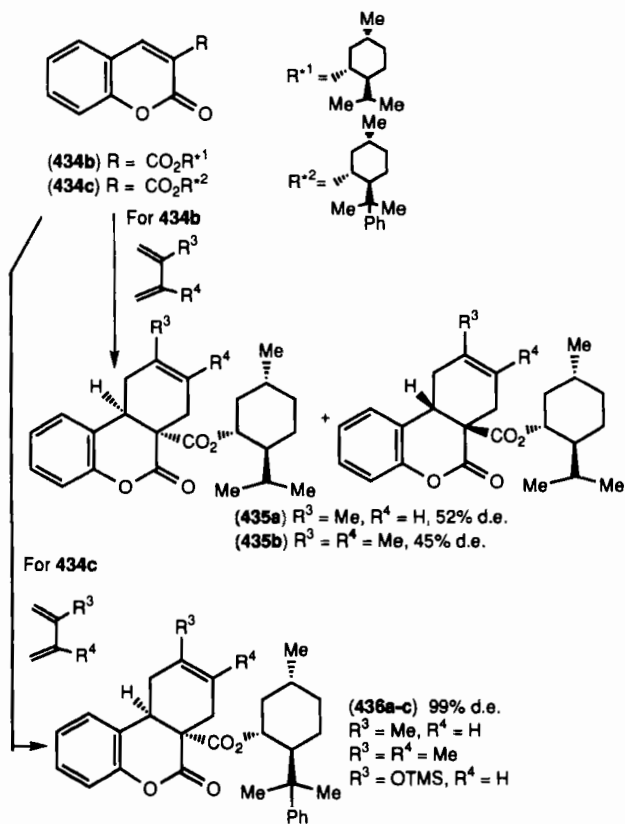
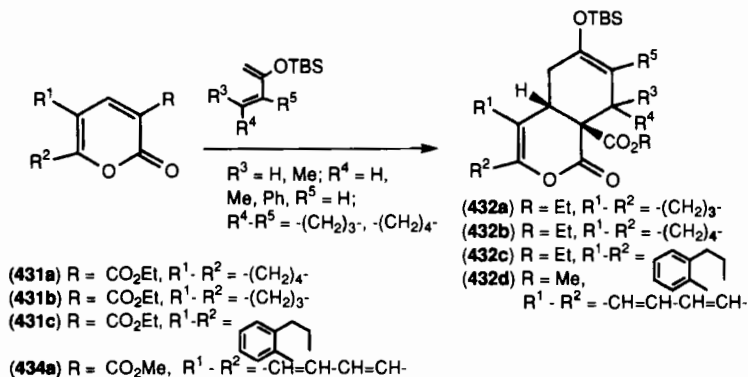
The similar annulation reactions of 3-ethoxycarbonyl-2-pyrones **431a–c** and 3-(alkoxycarbonyl)coumarins **434a** with 2-(trialkylsilyl)oxydienes give the cycloadducts **432a–d** (30–68%), as shown in Scheme 80.

Although coumarin **106a** reacts with 2,3-dimethylbutadiene only under forcing conditions ($260^\circ C$) and in the presence of a large excess of diene to give only a poor yield of the adduct (55JA1828), activated coumarin such as 3-methoxycarbonylcoumarin **434a** smoothly functions as a dienophile in the presence of Lewis acid ($ZnCl_2$) (93TL6575). Reaction of enantiomerically pure 3-(1-menthyloxycarbonyl)coumarin **434b** with isoprene and 1,3-dimethyl-1,3-butadiene gives the adducts **435a–b** in high chemical yields (52 and 45% d.e., respectively). Highly asymmetric Diels–Alder reactions (>99% d.e.) have been achieved between enantiomerically pure 3-(8-phenylmenthyloxycarbonyl)coumarin **434c** and 1,3-butadiene derivatives to give the adducts **436a–c** in high yields.

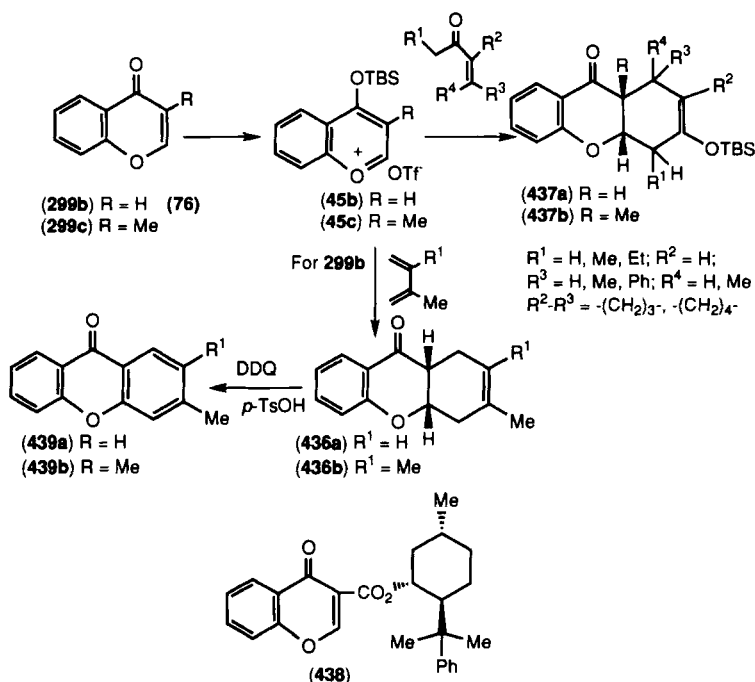


SCHEME 79

Treatment of chromones **299b–c** (Scheme 81) with *t*-butyldimethylsilyltriflate (TBSOTf) affords 4-*t*-butyldimethylsilyloxy-1-benzopyrylium salts **45b–c** (89H35). The pyrylium salts **45b–c** react with $R^1CH_2CO-CR^2=CR^3R^4$ [$R^1 = H, Me, Et$; $R^2 = H, R^3 = H, Me, Ph$; $R^2R^3 = (CH_2)_n$, $R^4 = H, Me$; $n = 3, 4$] and 1,3-butadienes in the presence of TBSOTf and 2,6-lutidine to give cycloadducts **436a–b** and **437a–b** in moderate to high yield. The ring fusion geometry of **436** and **437** has been determined to be *cis*. Highly asymmetric Diels–Alder reactions (98% d.e.) have been achieved between 3-(8-phenylmenthyloxycarbonyl)chromone **438** and 1,3-butadienes in high yield (94H1483). The reaction mechanisms are explained



SCHEME 80

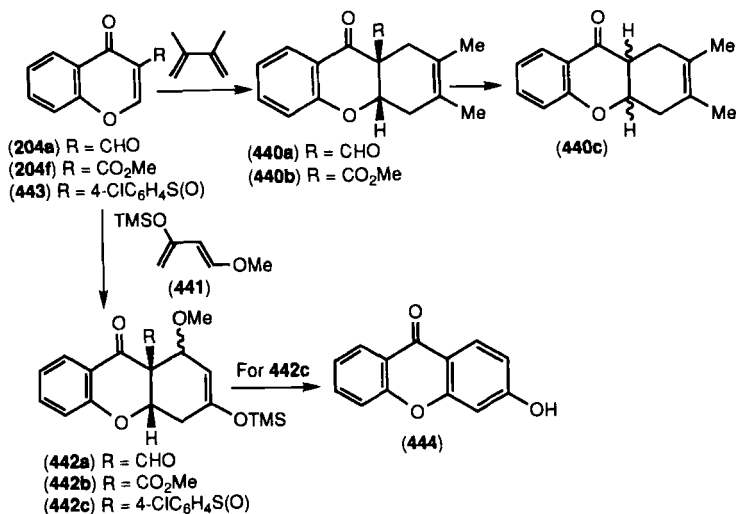


SCHEME 81

in terms of stereoelectronic and 1,3-allylic strain effects together with steric hindrance during the reaction (91JOC2058). Dehydrogenation of **436a–b** with DDQ and *p*-TsOH affords xanthenes **439a–b**.

As shown in Scheme 82, benzopyrones **204a,f** react with $\text{H}_2\text{C}=\text{CMeC}(\text{Me})=\text{CH}_2 in the presence of TiCl_4 to give the corresponding [4 + 2]-cycloadducts **440a–b**, the former undergoing facile deformylation to give **440c** and its C-9a isomer (87T3075). Benzopyrones **204a,f** undergo efficient uncatalyzed cycloaddition to $\text{MeOCH}=\text{CH}(\text{OSiMe}_3)=\text{CH}_2 **441** to give the respective adducts **442a–b** as mixtures of C-1 stereoisomers. Heating the 3-arylsulfinylchromone **443** with diene **441** affords 2-hydroxyxanthone **444** in 50% yield, the presumed cycloaddition–elimination sequence constituting a new route to the xanthone systems.$$

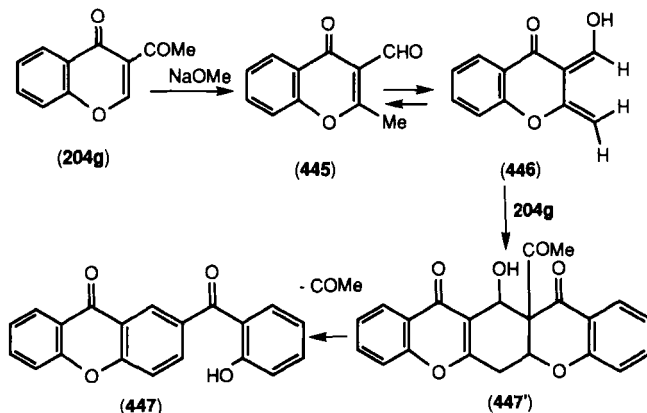
3-Acetylchromone **204g** (Scheme 83) undergoes base-catalyzed acyl–acyl rearrangement by MeONa to give the isomeric 3-formyl-2-methylchromone **445**, which is in tautomeric equilibrium with quinodimethane **446** (84CC1319; 93T4127). The Diels–Alder reaction of **446** with **204g** gives the adduct **447'**, which undergoes base-catalyzed elimination and deacylative elimination to give xanthone **447**.



SCHEME 82

E. [5 + 2]-ANNULATION REACTIONS

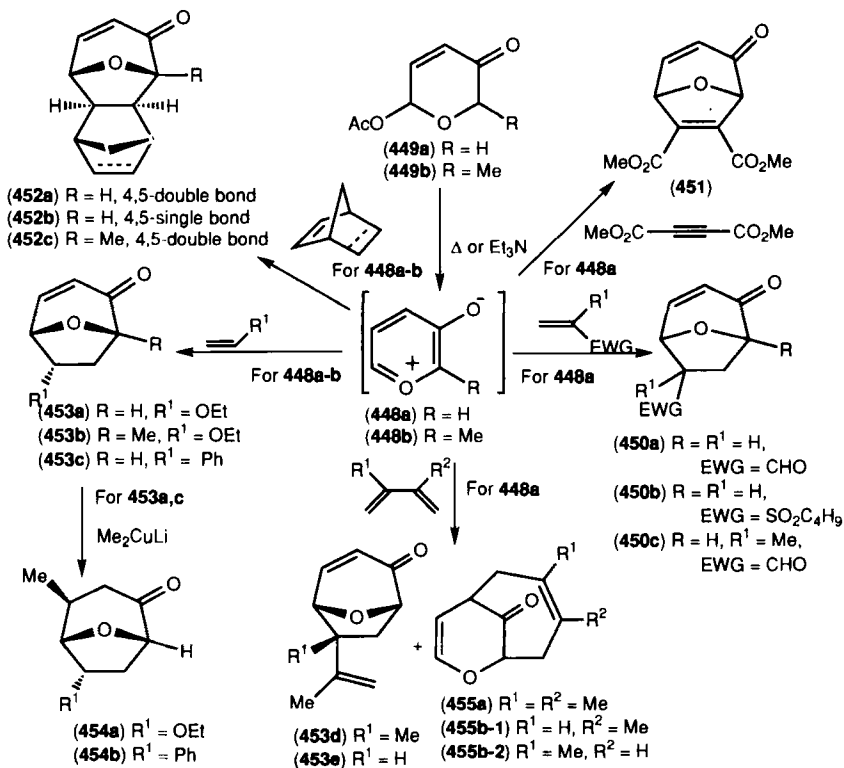
Whereas syntheses of three-, four-, and six-membered carbocyclic rings are often efficiently constructed by cycloaddition reactions, there are few analogous general routes to five- and seven-membered rings. Efficient, expeditious approaches to stereodefined seven-membered rings have been sought due to increasing awareness of the occurrence of these substructures in a wide variety of bioactive natural products, including guanine and



SCHEME 83

pseudoguinane sesquiterpenes, troponoids, and tumor-promoting diterpenes. Convenient methodology for the synthesis of a seven-membered ring involves trapping oxidopyrylium species **448** with various olefins. There have been reviews for the synthetic use of oxidopyrylium cycloadditions [76AG(E)1; 86G109].

The 3-oxidopyrylium intermediate **448a** (Scheme 84) is generated from the readily available 6-acetoxypyran-3(6*H*)-one **449a** by the action of heat (80JOC3361). Intermediate **448a** reacts with electron-deficient dipolarophiles, giving reasonable yields (35–69%) of the adducts **450a–c** (80JOC3359). Reaction of **449a** with dimethyl acetylenedicarboxylate via **448a** gives the adduct **451** in 42% yield. Base treatment of the acetates **449a–b** also gives the corresponding 3-oxidopyrylium species **448a–b** [83JCS(P1)1261]. Norbornadiene and norbornene react with acetate **449a–b** in the presence of triethylamine to produce the appropriate *exo*-cycloadduct **452a–c**. With norbornadiene, one major *exo*-adduct **452a** is



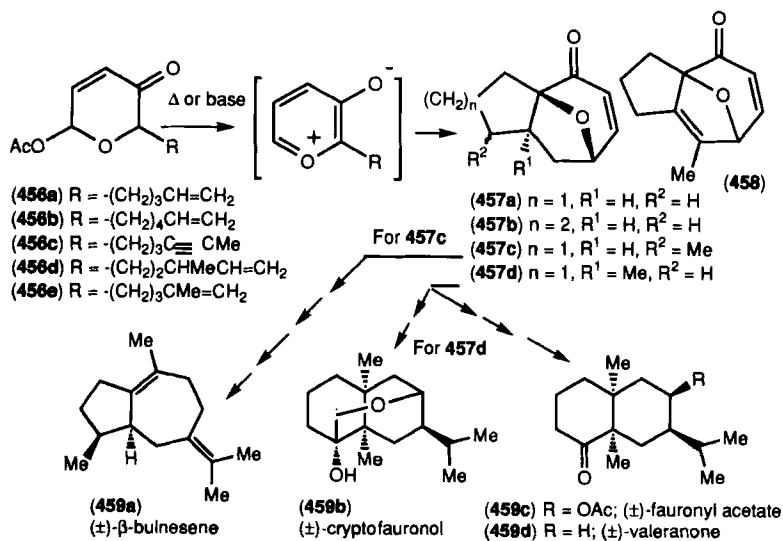
SCHEME 84

formed in 50% yield. Treatment of **449a–b** with $\text{EtOCH}=\text{CH}_2$ and styrene in the presence of Et_3N gives the *endo*-cycloadducts **453a–c** in 42–45% yield. The regioselectivity of the addition is that expected by a standard frontier molecular orbital argument. Lithium dimethylcuprate adds to the enone group of compounds **453a,c** in a stereospecific manner, the methyl group entering *syn* to the bridging oxygen atom to give the adducts **454a–b**, respectively.

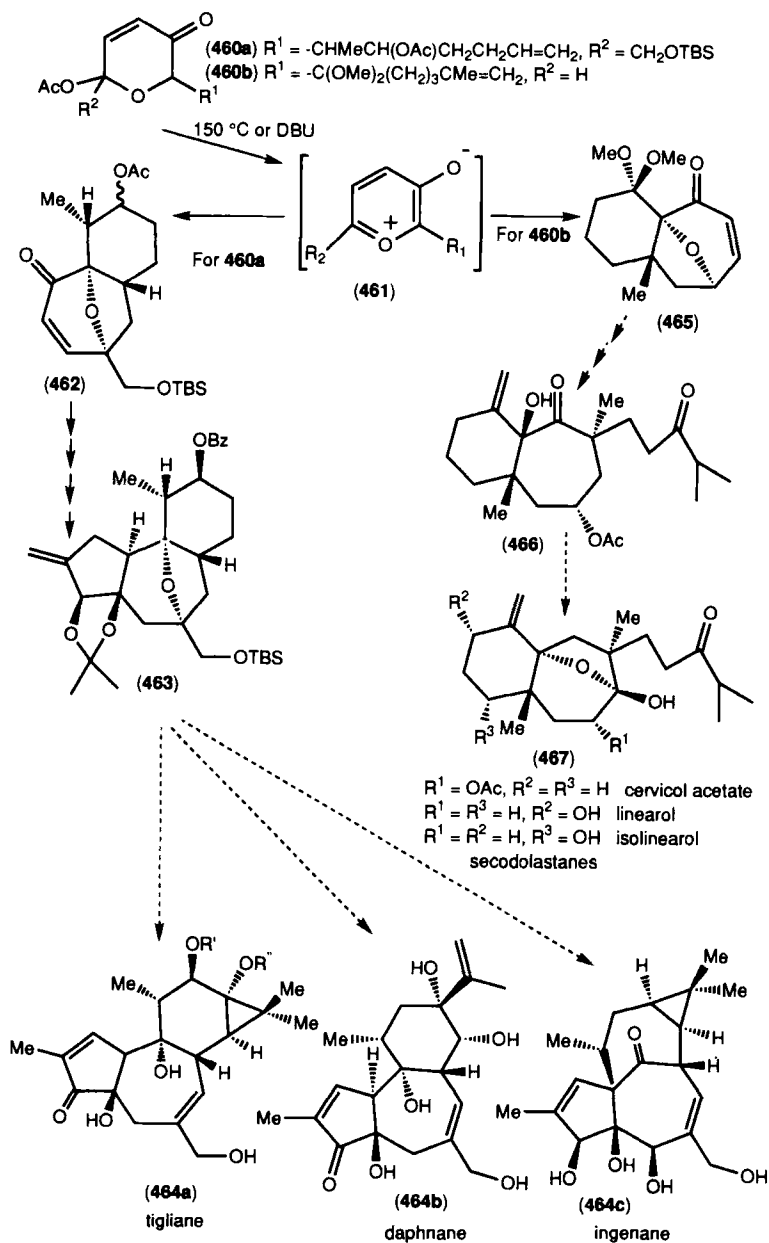
However, **449a** reacts with $\text{CH}_2=\text{CMeCMe}=\text{CH}_2$ in the presence of Et_3N to give a small quantity of the 2,6-adduct **453d** (8%) and the cycloadduct **455a** (49%) [83JCS(P1)1261]. In the presence of isoprene, two major components are isolated from the reaction products. Trapping across the 2,4-positions of the ylide gives a mixture of regioisomers (**455b–1** and **455b–2**, ratio 3:2) in 33% yield. A single 2,6-adduct whose structure is assigned to **453e** is formed in 29% yield, when $\text{R}^1 = \text{R}^2 = \text{H}$.

On heating in MeCN at 150°C for 16 h the oxopyrans **456a–c** give the oxatricycloalkanones **457a–b** and **458**, respectively. (See Scheme 85.) These reactions also proceed with base catalysts such as Et_3N or DBN (82CC1056). Some natural products, perhydroazulenes [(\pm)- β -bulnesene **459a**] and *cis*-fused 1-decalones [(\pm)-cryptofauronol **459b**, (\pm)-fauronyl acetate **459c**, and (\pm)-valeranone **459d**], are synthesized by this versatile method via **457c–d** from **456d–e**, respectively (83CC666).

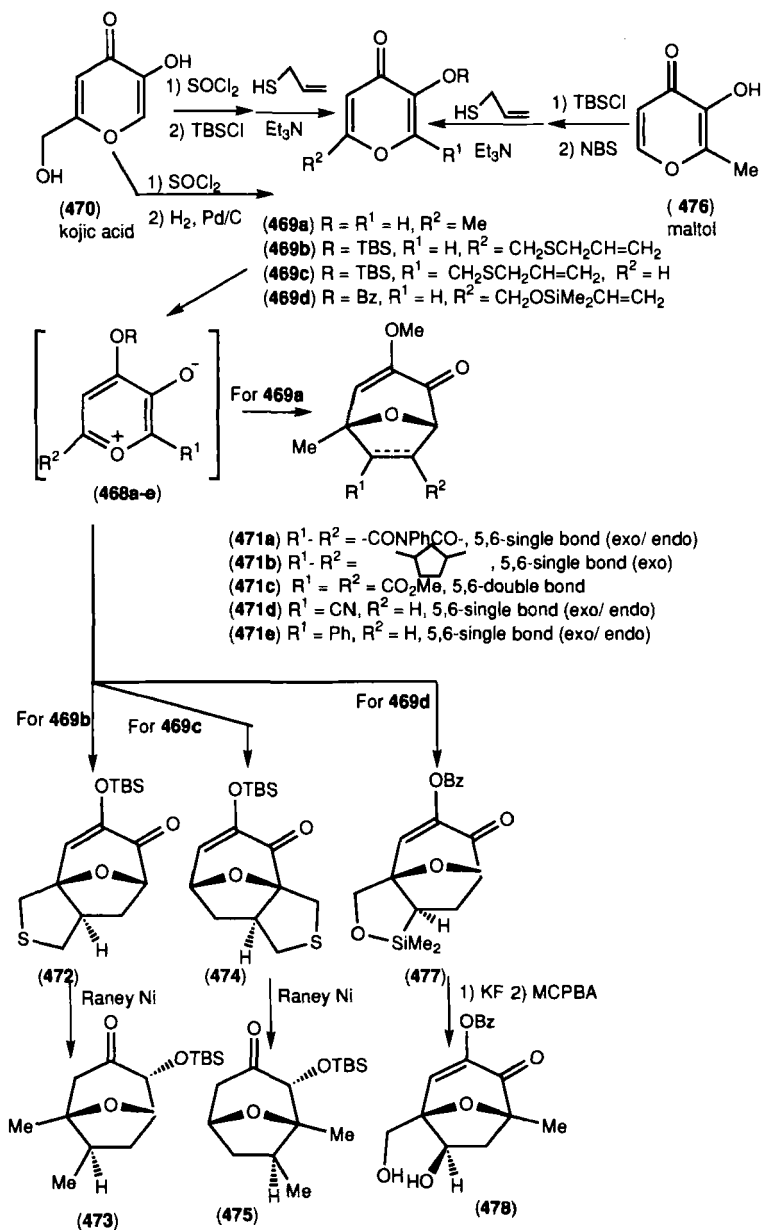
Smooth cyclization of **460a** (Scheme 86) occurs via 3-oxidopyrylium intermediate **461** at 150°C (CH_3CN) or DBU at ambient temperature to give



SCHEME 85



SCHEME 86



SCHEME 87

462 as a 2:1 mixture of C₁₂ epimers (92%) (89JA8954). The product (**462**) is converted via many chemical transformations into a general precursor **463** to the tigliane **464a**, daphnane **464b**, and ingenane **464c** diterpenes (89JA8957).

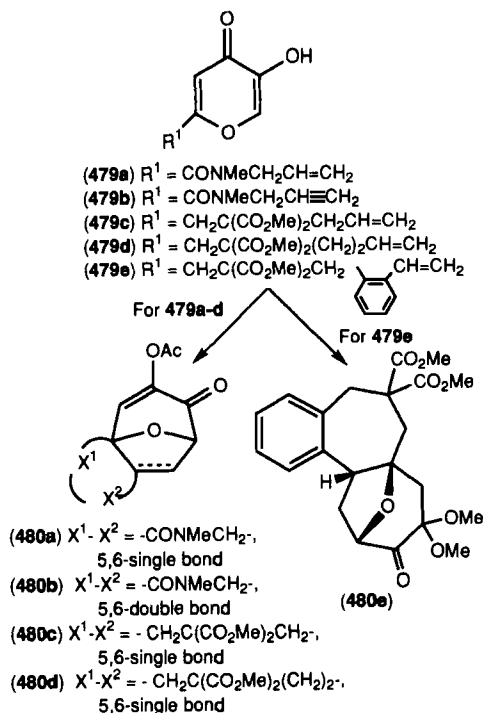
The [5 + 2]-intramolecular annulation of 3-oxidopyrylium ylide **461** prepared from the corresponding acetate **460b** by using DBU affords **465** (90TL6769). Transformation of **465** by way of several reactions gives the bicycloundecanone nucleus **466** of the secodolastane terpenes **467**.

4-Methoxy-6-methyl-3-oxidopyrylium ylide **468a** is prepared by way of **469a** from commercially available kojic acid **470** (92TL2115). (See Scheme 87.) Reaction of **468a** with *N*-phenylmaleimide in the presence of PhNMe₂ in CH₂Cl₂ gives 98% of imide **471a** (*exo:endo* = 1.8:1), whereas with norbornene the single *exo*-adduct **471b** is produced in 73% yield. The similar cycloaddition of **469a** occurs with dimethyl acetylenedicarboxylate, acrylonitrile (*exo:endo* = 2.3:1), and styrene (*exo:endo* = 1:2.2) to give the adducts **471c–e** in 73, 78, and 58% yields, respectively.

Thioether **469b** is prepared via three steps from kojic acid **470**. Heating **469b** in toluene (145°C, sealed tube, 40 h) gives the *exo*-adduct **472** in 71% yield (93JOC5585). Treatment of adduct **472** with Raney nickel in THF under reflux provides **473** (70%). A sequence similar to that for the synthesis of **473** leads to the bicyclic compound **475** in 52% overall yield by way of **474** from maltol **476**. Heating siloxane **469d** at 170°C gives adduct **477** followed by treatment with KF and *m*-chloroperbenzoic acid in DMF to give the oxabicycle diol **478** in 78% yield from kojic acid **470**.

As shown in Scheme 88, pyrolysis in refluxing solvent (benzene, acetonitrile) of 2-(ω -alkenyl or alkynyl)-5-hydroxy-4-pyrones **479a–d** bearing an olefin or acetylene moiety in the side chain gives intramolecular cycloadducts, followed by acetylation to isolate acetates **480a–d** in 42–70% yield (83TL1675). Treatment of **479e** with methanesulfonic acid (1.7 equivalents) in refluxing methanol for 12 h provides the ketal **480e** in 87% yield.

Pyrone **481a** is heated in a sealed tube for 3 days at 200°C to afford the cycloadduct **482a** as a single isomer in 74% yield (91JOC6267). (See Scheme 89.) However, **483a** gives only a trace amount of the desired cycloadduct. When **483c** in CH₂Cl₂ is treated with MeOTf at 20°C for 8 h, alkylation of the carbonyl oxygen occurs readily to give pyrylium salt **484**. When this salt in CH₂Cl₂/DMF is exposed to anhydrous cesium fluoride, the cycloaddition proceeds smoothly at room temperature to give cycloadducts **485a/485b** (3.8:1 mixture) in 84% yield. When **483b** in CH₂Cl₂ is treated with MeOTf for 11 h, pyrylium salt **484** is produced. Upon reaction at 20°C with the nonnucleophilic base 2,2,6,6-tetramethylpiperidine, **484** gives cycloadducts **485a/485b** (3.8:1, respectively, 82% yield). The same methods are applied



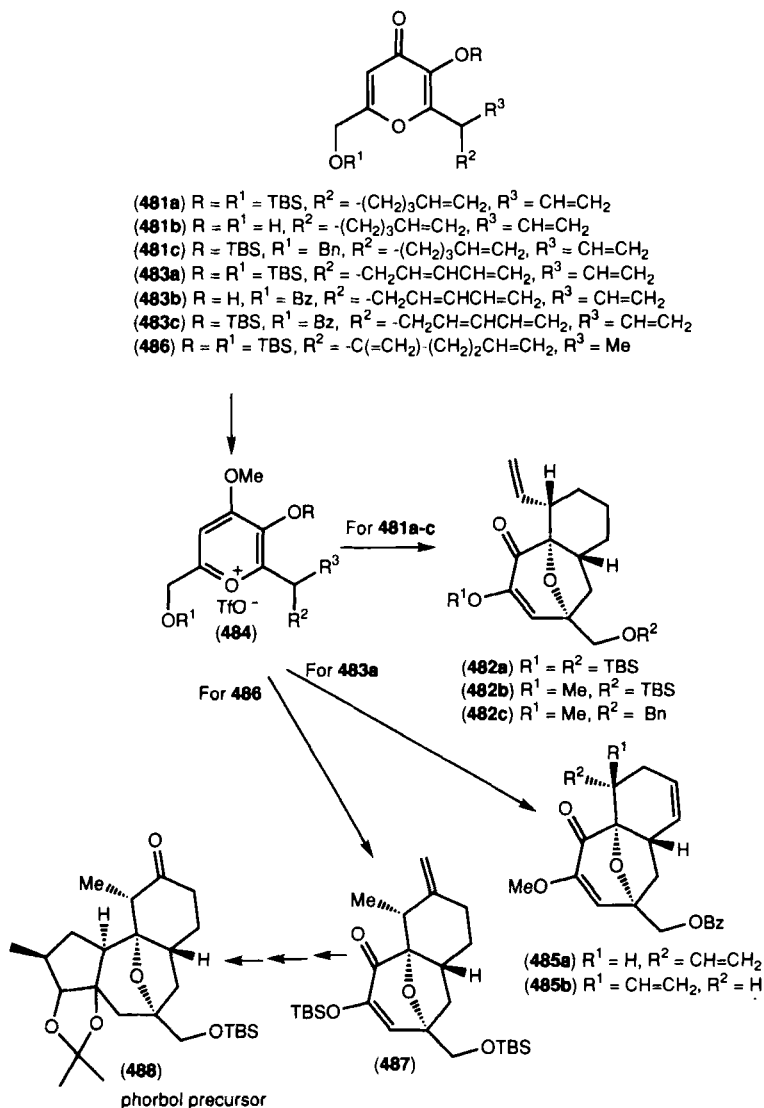
SCHEME 88

to pyrones **481b–c**. The respective cycloadducts **482b–c** are obtained again at room temperature in 83 and 88% yields a single isomers.

When a toluene solution of **486** is heated at 200°C for 48 h, the cycloadduct **487** is obtained as a single isomer (71%) (90JA4956). The synthesis of phorbol precursor **488** is achieved by using this group-transfer-induced cycloaddition.

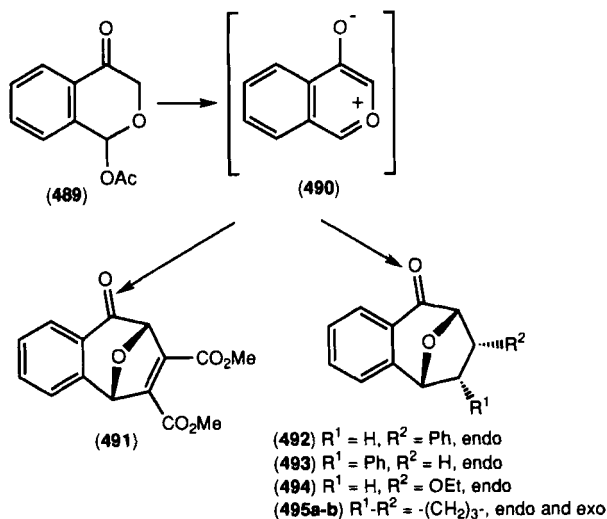
Treatment of acetate **489** (Scheme 90) with base or heat generates the reactive intermediate **490**, which is trapped with a wide range of dipolarophiles (84CC702). Dimethyl acetylenedicarboxylate gives 1:1 adduct **491** in 88% yield. With styrene two regioisomeric *endo*-adducts **492** and **493** are isolated in 48% and 37% yields, respectively. The reaction of **490** with ethyl vinyl ether gives the single *endo*-adduct **494** (60%), the reverse regiochemistry to that observed in the 3-oxidopyrylium series. Cyclopentene reacts with the ylide **490** to give *endo*-adduct **495a** (70%) and *exo* adduct **495** (8%).

As Scheme 91 shows, reaction of *o*-(MeO_2C) $\text{C}_6\text{H}_4\text{COCHN}_2$ **496** with a catalytic quantity of Cu(II) acetylacetonate in the presence of acetylenic



SCHEME 89

dipolarophiles gives cycloadducts **498a** (66%), **498b** (73%), **498c** (44%), **498d** (39%), **498e** (45%), **498f** (9%), and **498g** (13%) via reaction of the dipolarophiles with 1-methoxybenzo[c]pyrylium-4-olate **497a**, which is generated by the intramolecular carbene–carbonyl reaction of the corresponding carbene (79BCJ3582).

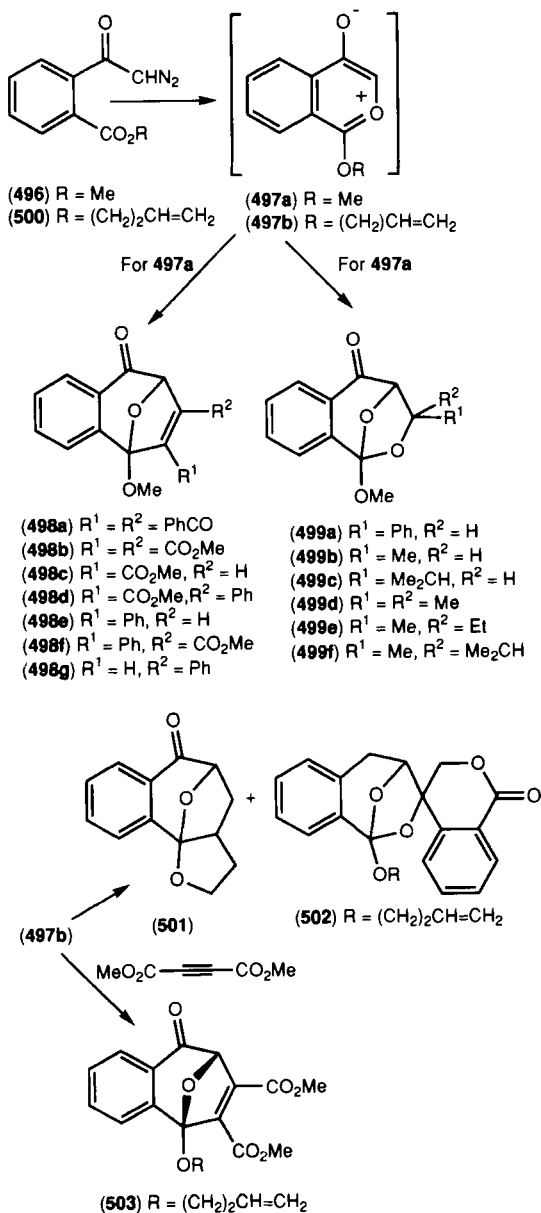


SCHEME 90

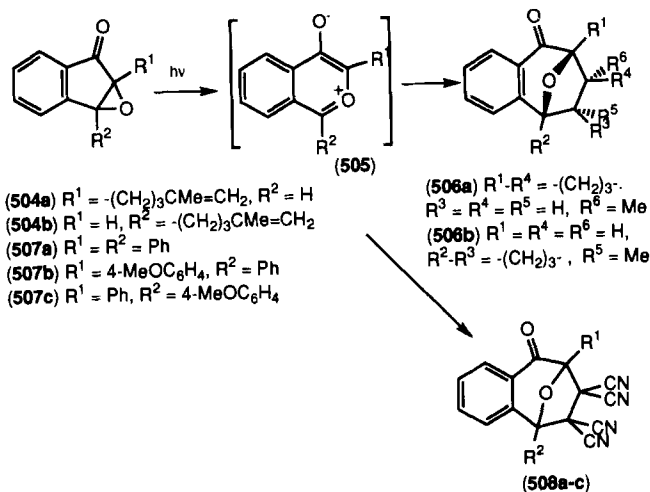
Cyclic orthoester 1,3-dipolar cycloadducts **499a-f** of benzopyrylium-4-olate **497a** are obtained in high yields with carbonyl reactants, starting from the Cu(II) acetylacetonate-catalyzed decomposition of **496**. The carbonyl compounds include substituted benzaldehydes, MeCHO, EtCHO, Me₂CHCHO, Me₃CCHO, acetone, MeCOEt, MeCOCHMe₂, (ClCH₂)₂CO, substituted acetophenones, benzoyl cyanides, cyclopentanone, cyclohexanone, 1-indanone, 9-fluorenone, anthrone, and anthraquinone. However, MeCOCMe₃ and Ph₂CO give no adduct (83CL1453; 85BCJ1787). Aldehydes and unsymmetric ketones give the *endo*- and *exo*-adducts. The regio-specificity of the 1:1 cycloaddition has been explained according to the frontier orbitals calculated by the STO-3G method.

Treatment of **500** with a catalytic quantity of rhodium(II) acetate at 25°C in benzene affords cyclopenta[1,2-*b*]furanone **501** (87%) via an oxidopyrylium ylide intermediate **497b** (88JA2894). In addition to **501**, spiroisochromanedione **502** is also produced in 10% yield. In the presence of excess dimethyl acetylenedicarboxylate, the only product obtained corresponds to the bimolecular dipolar cycloadduct **503**.

Irradiation (>300 nm; Pyrex) of aromatic epoxy ketones **504a-b** (Scheme 92) in benzene produces reactive intermediates **505** that can be efficiently trapped in an intramolecular manner by unactivated olefins in the side chain to give **506a** (65%) and **506b** (34%) (83TL5585). The quantum yields of photoisomerization of epoxydiarylindanones **507** to the benzopyrylium intermediate **505** have been determined to be 0.85, 0.80 and 1.00, respectively, following cycloaddition with TCNE to give **508a-c** (84KS167).



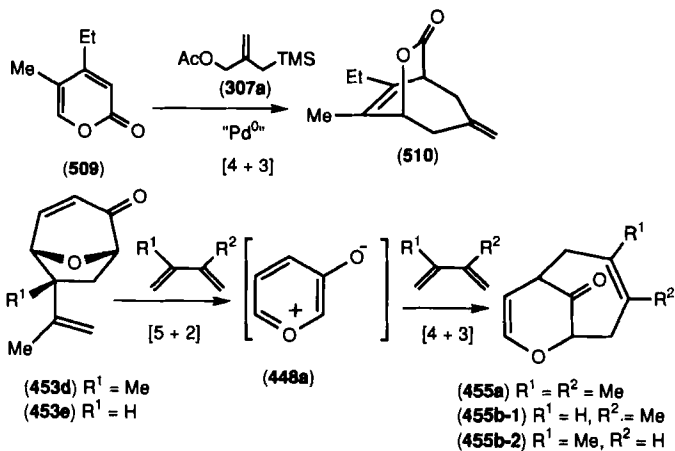
SCHEME 91



SCHEME 92

F. OTHER ANNULATION REACTIONS

Some annulation reactions other than those described above have been found. Reaction of 4-ethyl-5-methyl-2-pyrone **509** (Scheme 93) with the trimethylenemethane palladium complex derived from 2-trimethylsilylmethylallyl acetate **307a** gives the [4 + 3]-cycloadduct **510** in

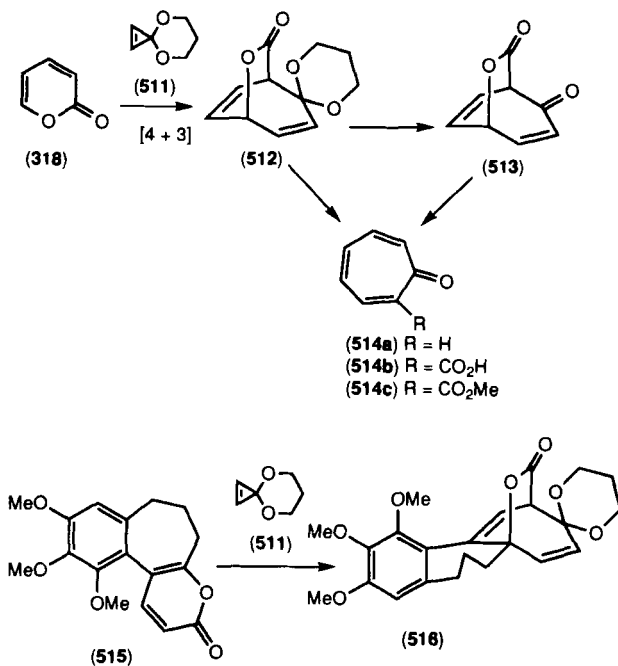


SCHEME 93

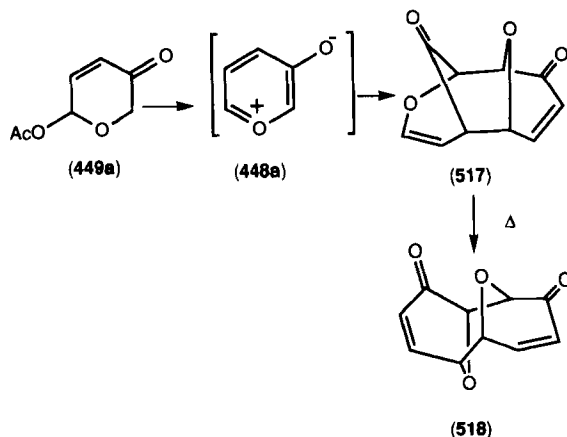
89% yield [89AG(E)213]. Reaction of **448a** with a conjugate diene in the presence of Et_3N gives [4 + 3]-cycloadducts **455a** (49%) and **455b** (33%) along with 2,6-adducts **453d-e** as minor [5 + 2]-cycloadducts [82CC1056; 83JCS(P1)126].

The thermal reaction (70°C, benzene, 22 h) of 2-pyrone **318** with cyclopropenone ketal **511** provides the [4 + 3]-cycloadduct **512** (50%) (85JOC3425; 86JA6695). (See Scheme 94.) Mild, aqueous acid treatment of **512** produces the bicyclopentone **513**. Thermolysis of **513** gives cycloheptatrienone **514a**. Extensive aqueous acid treatment of **512** provides cycloheptatrienone-1-carboxylic acid **514b** which affords 2-(methoxycarbonyl)cycloheptatrienone **514c** upon esterification. The thermal [4 + 3]-cycloaddition reactions of the cyclopropenone ketal **511** have been further confirmed in initial studies on their application to the total synthesis of colchicine utilizing Eschenmoser's 2-pyrone **515** to give **516**.

Treatment of **449a** (Scheme 95) with triethylamine at room temperature affords the dimer **517** in 68% yield via [5 + 3]-cycloaddition of the intermediate ylide **448a** (80JOC3361). Upon heating at 140°C for 7 h, the dimer **517** is transformed into the isomer **518**.



SCHEME 94



SCHEME 95

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